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POWDERED STOMACH IN TREATMENT OF FATTY LIVER AND OTHER MANIFESTATIONS OF INFANTILE PELLAGRA

ITS SIGNIFICANCE WITH REFERENCE TO THE PROBLEMS OF EDEMA AND STEATORRHEA IN INFANTS AND IN ADULTS

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The syndrome which we accept provisionally as pellagra in infants is prevalent among the non-European children in Johannesburg. An analysis of the hospital records during the last four years has revealed that the death rate among children suffering from this disease fluctuates between 40 and 60 per cent irrespective of the nature of the treatment administered. Even vitamin concentrates given parenterally did not in any way diminish this high mortality rate.

The views generally held concerning the causes of pellagra [1] seem to suggest that this disease is in some way caused by a lack of vitamin B complex, especially of nicotinic acid. However, the failure of vitamins in approximately 50 per cent of cases added support to our hypothesis that after a variable latent period a disease initiated by a dietary deficiency fails to respond when the factor whose deficiency is suspected to cause the disease is supplied liberally.

The rather complicated clinical picture presented by these children obliged us to search for that mechanism the disturbance of which could account for the edema, steatorrhea and other reactions frequently present in this disease. In a previous study [2] we indicated that the liver was invariably damaged to a greater or lesser extent, as shown by the accumulation of abnormal quantities of fat. Irrespective of the clinical state of the patients or the biochemical findings, the prognosis was largely determined by the severity of the hepatic injury, assessed by histologic examination of fragments of liver obtained by the aspiration biopsy technic.[3]

It soon became clear that the disturbances in the functions of the liver perhaps contributed in no small measure toward the production of many of the manifestations of infantile pellagra. By means of the aspiration biopsy technic we established beyond reasonable doubt that the fatty liver in pellagrins does not result from intercurrent infections but is one of the manifestations of dietary imbalance.

Experiments on animals indicated that, while the lack of a specific vitamin from the diet caused a fatty liver, the addition of this vitamin frequently failed to alleviate this pathologic process and in fact, under certain circumstances, even intensified the lesion.[4] It was also demonstrated that the fatty liver produced in animals by the lack of a vitamin could be cured by the addition of some substance other than the vitamin, namely, methionine.[5]

These findings in animals received confirmation from our studies of the effects of vitamins on the fatty livers of human infants suffering from pellagra. We were able to show that in infantile pellagrins with intensely fatty livers vitamin therapy could not reduce the death rate or heal the hepatic lesion. Even when hepatic damage was mild, although the clinical condition

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J. Inglis, L. Friedlander and E. Hammar of the Johannesburg General Hospital gave assistance.

1. Stannus, H. S.: Pellagra and Pellagra-Like Conditions in Warm Climates, Trop. Dis. Bull. **33**:729 (Oct.); 815 (Nov.) 1936. Elvehjem, C. A.: Relation of Nicotinic Acid to Pellagra, Physiol. Rev. **20**:249 (April) 1940.

2. Gillman, T., and Gillman, J.: Hepatic Damage in Infantile Pellagra and Its Response to Vitamins, Liver and Ventriculin Therapy as Determined by Repeated Liver Biopsies, to be published.

3. Gillman, T., and Brydon, J. G.: To be published.

4. Handler, P., and Dann, W. J.: Inhibition of Rat Growth by Nicotinamide, J. Biol. Chem. **146**:357 (Dec.) 1942.

5. Engel, R. W.: The Relation of B-Vitamins and Dietary Fat to the Lipotropic Action of Choline, J. Nutrition **24**:175 (Aug.) 1942. McHenry, E. W., and Patterson, J. M.: Lipotropic Factors, Physiol. Rev. **24**:128 (Jan.) 1944.

improved under therapy, the recovery of the liver was slow, and the patients left the hospital with residual damage to the liver. We discovered that powdered stomach led to a rapid improvement in the clinical condition and simultaneously depleted the fat from the liver.

The fact that powdered stomach, a substance not related to any of the known vitamins, was able to cure infantile pellagra afforded us an opportunity of examining the various mechanisms involved in the production of several of the clinical features of this disease in relation to the fatty liver.

The objects of this paper are, firstly, to record the clinical and biochemical findings in 23 cases of infantile pellagra before and after various forms of treatment; secondly, to assess the relation between the pathologic changes in the liver and the clinical picture; thirdly, to examine the factors responsible for the edema and steatorrhea prevalent in this disease, and, fourthly, to comment on the implications of the edema and steatorrhea in modifying the course of the disease. Finally, in view of the similarities between infantile pellagra and those other diseases of infants and adults characterized by steatorrhea, edema and anemia, we will attempt to show that all these diseases, though differently caused, probably follow the same course once the steatorrhea appears, owing to the disturbance of a similar physiologic mechanism.

MATERIAL

This report is based on the study of 23 infants and children suffering from pellagra who were admitted to the Johannesburg Non-European Hospital during the summer of 1943-1944 and the autumn of 1944.

Aspiration biopsies of the liver were performed on all these patients within a few hours of admission, and whenever possible blood was withdrawn for hematologic, biochemical and serologic examination. For 9 patients who passed bulky fatty stools estimations of the water and of the split and unsplit fat content were made. Examinations of urine were made in every instance to exclude severe renal damage.

Full clinical records of the history of the disease, diet and clinical signs were kept. The children were weighed on admission and daily thereafter during their stay in the hospital.

The first 7 patients were treated with vitamins orally and parenterally according to the details listed in the table. The next group of 7 were given injections of 5 cc. of liver extract rich in the Cohn (anti-pernicious-anemia) fraction [6] twice daily for ten days. The third group of 9 patients received 10 Gm. of powdered stomach [7] orally, together with 5 cc. of tenth-normal hydrochloric acid once daily. In view of the shortage of the drug, treatment with powdered stomach could be continued for only five days. All patients were fed a liberal diet.

Biopsy of the liver was performed on all the patients every seven to ten days after admission, and comparisons were made of the clinical progress and the changes in the histologic appearance of the liver.

CLINICAL FEATURES

The syndrome which was seen in the Johannesburg Non-European Hospital and which we regard as infantile pellagra is characterized by severe edema, typical cutaneous lesions, labial and angular stomatitis, glossitis, diarrhea or steatorrhea, peculiar depigmentation of the skin over the entire body and a graying of the hair of the scalp with varying degrees of alopecia.

A similar syndrome has been encountered in other parts of South Africa [8] but Trowell [9a] was the first to suggest that this syndrome called by different names was probably infantile pellagra.

Although Trowell [9a] and Kark [8d] have carefully recorded the majority of the features of this form of malnutrition in infants, there are several aspects of this disease which require further amplification, such as the seasonal incidence, the peculiar manifestations of some of the cutaneous lesions and, especially, the steatorrhea and the edema in relation to the hepatic damage, as revealed by the aspiration biopsy technic.

Seasonal Incidence.—An analysis of over 400 cases of infantile pellagra in patients of the Johannesburg Non-European Hospital extending over a four year period reveals that, while the disease occurs throughout the year, the

6. The preparation used was an injectable liver extract (Abbott Laboratories) containing 10 U. S. P. units per cubic centimeter.

7. The preparation given was ventriculin (Parke, Davis & Company).

8. (*a*) Williams, C. D.: Nutritional Disease of Childhood Associated with Maize Diets, Arch. Dis. Childhood **8**:423 (Dec.) 1933. (*b*) Purcell, F. M.: Diet and Ill-Health in the Forest Country of the Gold Coast, London, H. K. Lewis & Co., Ltd., 1939. (*c*) Macvicar, N.: Pellagra in the Cis-Kei, South African M. J. **9**:892 (Dec. 25) 1935. (*d*) Kark, S. L.: Adult and Infant Pellagra in South African Bantu: A Comparative Clinical Study, South African J. M. Sc. **8**:106 (July) 1943.

9. (*a*) Trowell, H. C.: Infantile Pellagra, Tr. Roy. Soc. Trop. Med. & Hyg. **33**:389 (Jan.) 1940; (*b*) Pellagra in African Children, Arch. Dis. Childhood **12**:193 (Aug.) 1937.

greatest incidence is during midsummer and the lowest during midwinter. In this respect pellagra in infants resembles the disease in adults in Johannesburg.

Dermatitis.—A description of the dermatologic reactions in infantile pellagra has been carefully recorded by Trowell and Kark.

In our selected series of 23 cases diffuse depigmentation associated with patchy pigmentation and scaling occurred in 10 patients, while in 4 there was ulceration of the buttocks, genitalia, legs, arms or trunk. An unusual and hitherto unrecorded lesion expressed itself as crops of dark brown raised spots on the upper and lower extremities, especially on the dorsal surfaces of the hands and feet. These spots closely resembled the purpuric eruption of onyalai, a thrombopenic purpura frequently observed among the patients in this hospital.[10] However, the bleeding time was normal, and the subsequent extension of the lesions, followed later by cracking and desquamation of the skin in the affected areas, left little doubt that these spots were merely another manifestation of the pellagrous rash.

In severe infantile pellagra the exfoliation of the skin may be so extensive and so acute that large portions of the body are denuded. The exposed areas are raw, red and oozing and frequently become secondarily infected. These septic wounds are associated with such severe collapse that they have repeatedly been mistaken for severe burns or scalds.

Tongue.—The raw, red beefy tongue of adult pellagrins is not seen in infants; instead the tongue is smooth and atrophic. A common phenomenon in adult pellagrins is an infiltration of the papillae on the tip, dorsum or sides of the tongue with black pigment. This has occasionally been recorded among colored races and has been regarded as a congenital abnormality or as a consequence of parasitic infections.[11] Kark regarded pigmentation of the tongue as a type of pellagrous glossitis. We have actually seen this pigment appearing during the healing of the raw, beefy tongue or of the magenta red tongue in avitaminosis. We are satisfied that this lesion is not a congenital abnormality, especially since we have never observed it in children under 10 years of age.

As we have already indicated, iron pigment first appears in considerable quantities in livers damaged by acute or long-standing chronic malnutrition in children over 9 years of age.[12] It is at this time, too, that the tongue also becomes pigmented. The metabolism of iron pigment undergoes a radical change at this age period (8 to 10 years), so that some forms of acute and chronic malnutrition may result in such a disturbance of intracellular metabolism in various organs and tissues in the body that iron-containing pigment is deposited in the hepatic cells and in the tunica propria of the tongue. We have already indicated that iron pigment deposited in the cells of the liver does not arise directly from destruction of blood but is formed in the cell itself.[12]

Edema.—Edema of varying severity can be regarded as a constant finding in infantile pellagrins. It was present in 27 out of 29 patients described by Trowell,[9a] and in 20 of 34 patients reported on by Kark the edema appeared in a severe form. In our series 21 patients manifested various degrees of edema. In nature and distribution this edema is similar to that described by Trowell, except that we never saw the edema abate before death and that in some boys the edema of the penis and prepuce was so severe that the generalized edema was attributed to renal failure resulting from a severe and prolonged paraphimosis. Before the disease was recognized in this hospital as infantile pellagra, circumcisions were frequently performed to relieve what was then regarded as a urethral obstruction. Many of these operations were attended by fatal results.

Liver.—Although one of the most consistent conditions seen at autopsy in children dying from severe nutritional edema is an intensely fatty liver,[9a] it is generally thought that this fatty change was a terminal event or the result of an intercurrent infection.

By means of the aspiration biopsy technic, we have established that a fatty liver is the most constant single pathologic reaction seen in infantile pellagra. It appears early in the disease and, as we shall indicate later, probably plays an important part in modifying the course of the disease. Even with the mildest symptoms we have never failed to find some degree of fatty change in the liver. Although the extent

10. Stein, H. B., and Miller, E.: Acute Thrombocytopenic Purpura Associated with Hemorrhagic Bullae, with Special Reference to Onyalai, South African J. M. Sc. **8**:1 (Feb.) 1943.

11. McGregor, L.: The Significance of the Butterfly Sign and of Tongue Pigmentation, Tr. Roy. Soc. Trop. Med. & Hyg. **30**:482 (Jan.) 1937. Sundaram, S. K.: The Butterfly Sign and Pigmentation of the Tongue, ibid. **30**:482 (Jan.) 1937.

12. Gillman, T., and Gillman, J.: The Mitochondrial Origin of Cystosiderin (Iron Pigment) in the Liver Cells of Pellagrins, Nature, London **154**:148 (July 29) 1944.

of the fatty change in the liver varied from case to case, we have found that the degree of accumulation of fat is a more reliable indicator of the severity of the disease and of the prognosis than any of the clinical or biochemical findings. Thus, for example, in case 1 (described in the table) the clinical picture suggested a mild deficiency disease, whereas the biopsy revealed a severe lesion. This case terminated fatally.

In a previous communication we grouped the different degrees of hepatic damage into three categories.[2] In the first we included those livers in which almost all the cells contained single, large fat globules; in the second, the livers were less severely damaged and the fat occurred either as smaller globules staining more intensely with sudan IV (scarlet red) than in the first category or as diffusely distributed, multiple fine droplets. Many cells did not contain any fat. In the last category the fat was present in the form of fine, scattered droplets and then in only a few cells.

Our previous studies demonstrate that children with livers of the third category usually recovered after any form of rational therapy irrespective of the severity of the clinical picture, whereas the patients with livers of the first and second category frequently died unless treated with liver extract or, better still, with powdered stomach. Recovery was always accompanied by a diminution in the fat content of the liver.

The accumulation of fat causes an enormous enlargement of the individual hepatic cells. It was to be expected therefore that in our patients the livers would be enlarged. In 18 of 23 cases the liver was distinctly palpable (as shown in the table), and in 15 it extended almost to the umbilicus. In 1 instance, however, histologically the liver was included in the first category but clinically this organ was not palpable.

It must be remembered that in some of these malnourished children the abdomen is so distended that it is impossible to palpate even a grossly enlarged liver. When the liver is palpable, its size can be regarded as an extremely valuable evidence in assessing the severity of the disease and in arriving at an accurate prognosis.

The main clinical features of 23 cases of infantile pellagra are summarized in the table. It is apparent from this table that the clinical features and the severity of the lesions may vary from case to case. Whereas severe and extensive edema are frequently associated with severe cutaneous lesions (cases 2, 7, 10, 11, 13, 15, 19), a mild dermatitis may occur despite the presence of severe edema (cases 3 and 18). In view of the other signs usually associated with a typical case of pellagra, we feel justified in regarding as pellagrins the 3 patients in whom the rash was absent (cases 1, 5 and 17). However, in the cases available to us the most frequent manifestations were a large fatty liver, edema of varying severity, dermatitis, angular and labial stomatitis and graying of the hair with varying degrees of alopecia.

Biochemical Observations.—Because of the difficulties in drawing blood from these emaciated or grossly edematous children it was not possible to conduct full biochemical studies on all the patients recorded here. However, hematologic investigations were conducted in 7 cases. Hemoglobin estimations were made with the Zeiss hemoglobinometer (100 per cent, 16 Gm. of hemoglobin per hundred cubic centimeters of blood). Some degree of microcytic anemia was present in all the children examined. The macrocytic anemia described by Trowell was not observed. The white cells showed no abnormality other than a slight leukocytosis with a relative lymphocytosis. Despite the extremely low concentrations of serum proteins encountered in many of the patients, the sedimentation rate (one hour Wintrobe method) was normal.

The serum proteins were in the main reduced, the reduction of the albumin fraction being most noticeable, with a consequent lowering of the albumin-globulin ratio.

In 14 of the 23 cases the stools were large, pale, fermenting, offensive and greasy. In 8 cases the stools were examined biochemically. The results are summarized in the table. In 7 cases the fat content was excessive, consisting of a large amount of split and unsplit fats. In view of Andersen's careful studies [13] it is not possible on the basis of the nature of the fat in the stool to attribute the origin of such a fatty stool either to malabsorption or to pancreatic deficiency. Such fatty stools in infantile pellagra have also been reported by Gillan,[14] Trowell [9b] and Kark.[8d]

RESPONSE TO THERAPY

Vitamn Therapy.—An analysis of the cases of infants with pellagra admitted to the Johannesburg Non-European Hospital during the last

13. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: A Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344 (Aug.) 1938; Cystic Fibrosis of Pancreas, Vitamin A Deficiency and Bronchiectasis, J. Pediat. **15**:763 (Dec.) 1939.

14. Gillan, R. V.: Investigation into Certain Cases of Oedema Occurring Among Kikuyu Children and Adults, East African M. J. **11**:88 (June) 1934.

Case Number	Age, Years	Sex	Duration of Illness, Weeks	Diarrhea	Character of Stool	Cheilosis	Angular Stomatitis	Glossitis	Cutaneous Lesions	Edema	Size of Liver	R. B. C. Count	Hemoglobin, per Cent	Sedimentation Rate	Serum Protein: Albumin	Serum Protein: Globulin	Serum Protein: Total Protein	Wassermann Reaction	Stools: Water Content, per Cent	Stools: Total Fat, per Cent	Stools: Unsplit Fat, per Cent	Category of Liver Microscopically	Treatment	Result
1	2 6/12	F	2	+ +	F.	+	+	+	0	1	1	....	..	..	1.9	1.1	3.0	.....	..	..	..	I	Nicotinic acid and thiamine and vitamin C by injection; brewers' yeast and a halibut liver oil preparation orally	Died
2	1 12/12	F	6	+ +	B.	+ +	+	+	4.4	4.4	3	....	..	..	2.0	1.9	3.9	.....	..	..	..	I	Brewers' yeast, orange juice and a halibut liver oil	Died
3	1 8/12	F	4	+	F.	+	+	+	2.2	4.4	0	3.06	53	3	1.9	1.6	3.5	Neg.	83	52	0	II	Nicotinamide, thiamine hydrochloride, vitamin C; all by injection	Died
4	1 5/12	P	4	+	F.	+ +	+ +	+ +	3.2	1.2	0	4.2	60	6	...	...	...	Neg.	76	54.3	0	II	Full ward diet.....	Died
5	9/12	M	3	+ +	F.	+ +	+ +	+ +	0	1.1	0	4.4	80	4	2.2	1.2	3.4	Neg.	86.5	54	32	I	Riboflavin and nicotinamide by injection	Died
6		F	3	+	B.	+	+	+	4.2	0	1	4.2	80	12	...	...	...	.....	...	29	15	I	Full ward diet.....	Died
7	3 9/12	F	2	+ +	F.	+ +	+ +	+ +	0	4.3	2	...	...	...	2.5	1.6	4.1	Neg.	...	...	...	I	Full ward diet.....	Died
8	1	F	3	+ +	B.	+ +	+ +	+ +	4.1	2.4	2	...	...	...	1.8	2.9	4.7	Neg.	...	...	...	I	Liver extract by injection...	Died
9	2	F	3	+	B.	+	+	+	2.4	0	2	...	...	...	1.7	2.6	4.3	Neg.	...	...	...	I	Liver extract by injection...	Died
10	1	M	2	0	...	0	+	0	1.4	4.3	2	3.66	66	11	2.0	1.6	3.6	Neg.	...	...	...	III	Liver extract by injection...	Died
11	2	M	3	+ +	G.	+ +	+ +	+ +	4.3	4.4	2	3.2	60	7	2.5	1.0	3.5	Neg.	...	...	...	I	Liver extract by injection...	Recovered after 24 days
12	1 9/12	F	3	+ +	E.	+ +	+ +	0	4.2	4.4	2	3.96	53	8	2.0	1.6	3.6	Neg.	...	...	...	I	Liver extract by injection...	Recovered after 30 days
13	4	F	2	+	F.	+	+	+	2.3	3.1	2	...	...	...	2.5	1.1	3.6	Neg.	83	38	25	II	Liver extract by injection...	Recovered after 26 days
14	3	M	4	+ +	G.	+ +	+ +	+	4.3	4.4	2	....	..	..	2.1	2.4	4.5	.....	..	..	..	II	Liver extract by injection...	Recovered after 35 days
15	2 5/12	M	3		F.			0	3.2	3.3	2	....	..	..	2.4	2.6	5.0	Neg.	84	33	29	II		
16	3	F	4		F.		+	0	4.4	4.4	1	....	..	..	....	....	....	.....	..	..	..	I	Liver extract by injection...	Recovered after 32 days
17	1 9/12	F	1	+	F.	+	+	0	3.2	3.3	2	....	..	..	1.8	1.8	3.6	Neg.	..	..	..	III	Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 17 days
18	2 4/12	M	3	+	F.	+	+	+	0	2.2	0	....	..	..	1.4	2.4	3.8	.....	..	..	..	II	Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 19 days
19	1 7/12	M	4	+	F.	+	+	+	1.1	3.3	3	....	..	..	....	....	....	.....	80	52	30	I	Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 14 days
20	1 11/12	M	1	+	...	+	+	+	3.2	4.3	3	....	..	..	2.0	1.9	3.9	Neg.	82	21	24	I	Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 21 days
21	2	F	2	+	F.	+	+	0	2.3	2.2	0	....	..	..	2.4	1.8	4.2	Neg.	..	..	..	II	Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 10 days
22	2 8/12	M	3	+	F.	+	+	+	4.4	1.1	2	....	..	..	....	....	....	.....	..	..	..	I	Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 10 days
23	1 9/12	M	1	+	F.	+	+	+	1.3	2.2	2	....	..	..	....	....	....	.....	..	..	..	I	Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 14 days
																							Powdered stomach 10 Gm. 5 cc. N/10 HCl	Recovered after 18 days

The code for the symbols and figures in the table is as follows:

Cutaneous lesions
Extent: (first digit in column)
1 = buttocks and genitalia only
2 = buttocks and legs and feet
3 = buttocks and legs and feet and shoulders and hands
4 = buttocks and legs and feet and shoulders and hands and face
Severity of cutaneous lesions: (second digit in column)
0 = dry skin
1 = bronze spots
2 = plaques
3 = desquamation
4 = ulceration

Edema
Extent: (first digit in column)
1 = feet and ankles
2 = feet and ankles and genitalia
3 = feet and ankles and genitalia and hands and arms
4 = feet and ankles and genitalia and hands and arms and face and eyelids
Severity: (second digit in column)
1 = just pitting
2 = moderate
3 = gross edema
4 = eyes occluded

Liver Size:
0 = not palpable
1 = just palpable
2 = below costal margin 2 to 3 fingerbreadths
3 = to umbilicus or below
Microscopic classification:
1st category
2d category
3d category
Character of stools:
G. = green B. = bloody F. = fatty

four years reveals a 40 to 60 per cent mortality [15] —and this despite the administration of both vitamins and a full diet. Our own studies indicate that, no matter how severe the clinical manifestation of the disease, provided the liver is not severely damaged the patients will recover on any form of rational therapy. The greatest difficulty presented by these children is their loss of appetite. Provided they take their feedings they usually recover, albeit slowly. In the presence of severe hepatic damage the response to vitamin therapy is erratic and most unsatisfactory. This is the experience of Youmans and associates [16] and Trowell.[9] It is our impression from the cases recorded here that massive doses of vitamins administered orally or parenterally tend to hasten the progress of the disease. All of the 7 patients treated with vitamins during this study died. In many we observed the desquamation of the skin following the administration of nicotinic acid, but the patients still died. Similar results with nicotinic acid therapy have been recorded by Trowell. Vitamin therapy failed to improve the liver, and, in view of the experimental evidence presented by Handler and Dann [4] in animals and our own observations on human infants, it would appear that the administration of massive doses of nicotinic acid and other crystalline vitamins is contraindicated in cases of severe infantile pellagra.

Liver Therapy.—Our results with liver therapy were considerably better than those with vitamins. Five of the 7 children lived.

The first sign of recovery was the gradual loss of edema fluid. The child looked brighter after two to three days' therapy, and the appetite improved. After five days' treatment the oral lesions commenced to heal, and the skin started peeling.

The liver improved more slowly than the clinical condition, and even at the end of three to four weeks when the children were discharged as clinically normal, there was a considerable degree of residual liver damage as seen histologically from the biopsy specimen.

In view of the 2 deaths of patients treated with liver extract and of the slow response in those children who recovered, we did not consider that liver therapy was entirely satisfactory.

Several other methods of therapy have been tried. Blood and serum transfusions were of no avail. One patient, a child of 9, was treated with 150 to 200 Gm. of fresh, raw, minced beef pancreas daily. This was administered through a gastric tube. The method is cumbersome and tedious, and, although we persisted with this treatment for two weeks, the response was very slow. The liver underwent considerable improvement during the first ten days but showed no change thereafter despite the continuance of therapy. The edema, too, improved slowly. The response to raw pancreas as seen in this single case was similar in many respects to that obtained with large doses of liver extract administered parenterally.

Treatment with Powdered Stomach.—In a previous paper we demonstrated that powdered stomach has a remarkable lipotropic action on the fatty livers of infantile pellagrins. Coincident with the rapid disappearance of fat from the liver there was also a remarkable improvement in the clinical picture.

Within twenty-four to forty-eight hours of the exhibition of dried hog's stomach there was a sudden loss of edema fluid. Eyes which were previously occluded by edema opened overnight. The edema of the limbs and genitalia disappeared so rapidly that the children frequently lost between 1 and 3 pounds (454 to 1,307 Gm.) in weight in twenty-four to forty-eight hours. The cutaneous and oral lesions healed surprisingly quickly, and within three to four days of the first dose of powdered stomach the skin commenced to desquamate, and within seven to ten days the skin appeared normal. The diarrhea and steatorrhea ceased within two to three days. The children rapidly lost their peevishness and irritability; they regained their appetites and ate well and on clinical grounds could be regarded as cured within ten to fourteen days.

As we have already shown, the livers recovered rapidly and were almost normal when the patients were discharged.

Although powdered stomach was administered for only five days, the improvement continued after therapy was suspended. We feel convinced that had it been possible for us to continue our treatment for a few more days even the small amount of fat remaining in the liver would have been completely removed and recovery might have been even more rapid. In view of our results we have no hesitation in regarding powdered stomach as a life-saving drug in the treatment of severe infantile pellagra. The rapid improvement in the clinical condition and the nervous symptoms as well as the almost immediate loss of edema fluid and the cessation of

15. Gillman, T.: Diet and Disease in Bantu Children, South African J. M. Sc., to be published.

16. Youmans, J. B.; Bell, A.; Donley, D., and Frank, H.: Endemic Nutritional Edema: Serum Proteins and Nitrogen Balance, Arch. Int. Med. **51**:45 (Jan.) 1933.

the diarrhea and steatorrhea move us to suggest that powdered stomach may be of considerable value in the treatment of allied diseases in infants, especially celiac disease and other steatorrheas, nutritional edemas, infantile atrophy and pink disease. Our reasons for this opinion will become patent from the following comment.

COMMENT

The syndrome of infantile pellagra described by Trowell and later by Kark and confirmed by our own study is widely prevalent in Africa.[17] There are several other diseases of unknown cause in which many of the features are indistinguishable from those seen in infantile pellagra. The most striking in children are celiac disease,[18] infantile atrophy,[19] cystic fibrosis of the pancreas [13] and nutritional or war edema.[20] Among adults, sprue and idiopathic steatorrhea [21] are also characterized by bulky fatty stools, edema and, post mortem, by a fatty liver.

Although the causes of all these diseases are unknown, the diseases have one feature in common—they all improve to a variable extent after treatment with liver extract.[22] In recent years it has been suggested that a nutritional imbalance is directly or indirectly responsible for the initiation of these diseases.[23]

The evidence available leaves little doubt that infantile pellagra is an expression of severe malnutrition. This disease may become manifest soon after the children are weaned and can be related to the inadequate diet. However, once the disease is established it responds erratically to dietary treatment. The failure of vitamin therapy of this disease is being recognized by an increasing number of investigators.[24] From our careful study of the reactions of the liver during therapy with vitamins, liver and powdered stomach, we are led to conclude that, although this disease is initiated by a dietary imbalance secondary pathologic changes soon supervene and the disease can no longer be alleviated by a full diet and vitamin concentrates. The mental symptoms, cutaneous lesions, glossitis, anemia, edema and steatorrhea are in our opinion immediately related, not to the initial malnutrition, but to the secondary pathologic processes resulting from attempts by the organism to readjust its metabolism to the deficient diet.

We have already adduced cogent evidence to substantiate this opinion from our analysis of the response of the fatty liver to therapy.[2] This view is strengthened by a critical analysis of the origin of the edema and steatorrhea and their disappearance after the administration of powdered stomach.

The cause of the extensive edema in infantile pellagra, celiac disease, infantile atrophy, nutritional edema, sprue and cystic fibrosis of the pancreas has been the center of much controversy. Some investigators regard this edema as resulting from severe protein deficiency,[25] while others consider it to be a manifestation of beriberi.[26]

It is known that low serum protein levels may be attended by edema.[27] In infantile pellagra, although the serum proteins are often reduced, the extent of this reduction by no means bears any relation to the extent or the severity of the edema. In case 1, with a total serum protein content of 3 Gm. per hundred cubic centimeters there was only a mild edema of the feet and ankles. In case 9, on the other hand, there was an extensive edema of both upper and lower extremities, and the eyes were completely closed by the edematous eyelids. The total serum pro-

17. Kark.[8d] Trowell.[9]

18. (*a*) Parsons, L. G.: Celiac Disease, Am. J. Dis. Child. **43**:1293 (May) 1932; (*b*) Coeliac Disease, in Parsons, L. G., and Barling, S.: Diseases of Infancy and Childhood, London, Oxford Universitiy Press, 1933, vol. 1, p. 363.

19. Maitland-Jones, A.: Infantile Atrophy, in Parsons, L. G., and Barling, S.: Diseases of Infancy and Childhood, London, Oxford University Press, 1933, vol. 1, p. 363.

20. (*a*) Waring, J. I.: Nutritional Heart Disease in Children, Am. J. Dis. Child. **55**:750 (April) 1938. (*b*) Gounelle, H.; Marche, J., and Bachet, M.: The Blood Protein in Famine Oedema, Nutrition Abstr. & Rev. **12**:611 (April) 1943.

21. (*a*) Manson-Bahr, P.: The Dysenteric Disorders, ed. 2, London, Cassell & Company, Ltd., 1943. (*b*) Molina, R. R.: Sprue in Puerto Rico: A Clinical Study of One Hundred Cases, Puerto Rico J. Pub. Health & Trop. Med. **17**:134 (Dec.) 1941; (*c*) Sprue in Porto Rico—Ten Years Later, ibid. **18**:314 (March) 1943.

22. Parsons.[18b] Maitland-Jones.[19] Manson-Bahr.[21a] Hamilton-Fairley, N.: Tropical Sprue, in Rolleston, H.: British Encyclopaedia of Medical Practice, London, Butterworth & Co., Ltd., 1939, vol. 11, p. 419.

23. Parsons.[18b] Manson-Bahr.[21a]

24. Trowell.[9a] Youmans, Bell, Donley and Frank.[16] Normet, L.: Report on the Pathogenesis of the Oedema of Annam and Deficiency Diseases, Bull. Acad. de méd., Paris **117**:239 (Feb.) 1937.

25. Liu, S. H.; Chu, H. I.; Wang, S. H., and Chung, H. L.: Nutritional Edema, Chinese J. Physiol. **6**:73 (Feb. 15) 1932; cited by Trowell.[9a]

26. Wheeler, G., in discussion on Youmans, J. B.: Endemic Nutritional Edema in Tennessee: Public Health Problem, South. M. J. **26**:713 (Aug.) 1933.

27. Weech, A. A., and Ling, S. M.: Relation of Serum Proteins to Occurrence of Nutritional Edema and to the Effect of Inorganic Salts, J. Clin. Investigation **10**:869 (Oct.) 1931. Lepore, M. J.: Edema Produced by Plasma Protein Depletion (Plasmapheresis), Arch. Int. Med. **50**:488 (Sept.) 1932.

tein content in this patient (4.7 Gm. per hundred cubic centimeters) was almost within the lower limits of normality, the albumin moiety being almost identical with that in case 1. This lack of correlation between the level of the serum proteins and the severity of the edema in malnutrition substantiates the views of Youmans and associates [16] and of Gounelle, Marche and Bachet.[20b]

It is known that the liver plays an important direct role in water metabolism quite apart from its effects on serum protein.[28] Selye, Collip and Thomson,[29] in a series of carefully planned experiments, have shown that intravenous injection of isotonic solution of sodium chloride into partially hepatectomized rats leads to the development of a diffuse edema associated with the accumulation of fat in the residual portion of the liver. If a venesection is performed on these partially hepatectomized animals that have been given transfusions, the edema can be prevented, although some fat still appears in the liver. Moreover, they demonstrated that partial hepatectomy inhibits the diuresis which invariably followed the transfusion of saline solution in normal animals. It follows from these experiments that the administration of fluids to animals with hepatic insufficiency leads to visible disturbances in the surviving portions of the liver and impairment of renal function associated with severe edema. These experiments indicate that the liver is directly concerned in water metabolism and that the disturbances in water metabolism in hepatic disease may in themselves aggravate the initial lesion in the liver.

This evidence from experimental work in animals as well as our observations on children suffering from infantile pellagra throws new light on the cause of the edema in malnutrition.

We have established in our previous study that the liver in infantile pellagra can be almost avascular. The sinusoidal bed is virtually occluded; the portal veins are small, and it was with the greatest difficulty that we were able to identify even the largest radicles of the hepatic vein. Judging from the degree of avascularity, it appeared in many instances as if the infant were almost hepatectomized. The vascular bed of the normal liver is enormous. In preliminary experiments which we have conducted with adult livers we have demonstrated that the large hepatic veins are capable of holding at least 500 cc. of fluid. Moreover, by injectional methods we have established that the vascular bed of the normal adult human liver may, without distention, accommodate over 800 cc. of fluid. When the vascular bed of the liver becomes occluded, as in infantile pellagra, the volume of blood which would normally be contained in hepatic vessels must now be displaced into the systemic circulation. This addition to the circulating blood volume in the absence of normal renal function probably contributes to the displacement of fluid into the tissues.

Jones and Eaton [30] have recorded the occurrence of a diuresis which precedes by several days other signs of recovery from hepatic disease. Under treatment with powdered stomach the liver of an infantile pellagrin improves in a remarkable fashion.[2] This improvement is associated with a rapid diminution in the edema resulting from a diuresis, which may lead to loss of 20 ounces (566 Gm.) of body weight in forty-eight hours. The rapid diuresis which heralds the sudden recovery of patients treated with powdered stomach suggests that the improvement in the liver is associated with the reestablishment of conditions conducive to renal function. In view of all this evidence there seems little doubt that the edema in infantile pellagra is intimately related in an inexplicable fashion to the extensive hepatic damage which we have demonstrated to be a constant feature in this disease.

The rapid subsidence of the edema with treatment with powdered stomach indicates that the stomach too, in some way, plays an important part in water metabolism. Petri and associates [31] noted the occurrence of edema in gastrectomized young swine. Since the stomach is almost invariably implicated to a greater or lesser extent in pellagra [32] and since, as we shall see later,

28. Adolph, E. F.; Gerbasi, M. J., and Lepore, M. J.: Redistribution of Water Following Transfusions and Infusions, Am. J. Physiol. **107**:647 (March) 1934. Crandall, L. A., and Roberts, G. M.: Increased Water Exchange Following Eck Fistula in Dogs, ibid. **117**: 318 (Oct.) 1936.

29. Selye, H.; Collip, J. B., and Thomson, D. L.: Some Interrelations Between Water and Fat Metabolism in Relation to Disturbed Liver Function, Lancet **2**:297 (Aug. 10) 1935.

30. Jones, C. M., and Eaton, F. B.: The Prognostic Significance of Spontaneous Diuresis in Acute and Subacute Disease of the Liver, New England J. Med. **213**:907 (Nov. 7) 1935.

31. Petri, S.; Norgaard, F., and Bing, J.: Pathological Changes Produced by Gastrectomy in Young Swine, Am. J. M. Sc. **195**:717 (June) 1938.

32. (*a*) Flinker, R.: The Function of the Stomach in Pellagra, Arch. f. Verdauungskr. **57**:282 (May) 1935. (*b*) Rubio, D. M.: Studies in Pellagra: I. The Gastric Secretion, Trop. Dis. Bull. **40**:79 (Jan.) 1943. (*c*) Gillman, T.: Critical Evaluation of Neutral Red Excretion and Acid Secretion Tests of Gastric Function in the Normal and in Subjects with Gastric Disorders, Gastroenterology **3**:188 (Sept.) 1944.

the interference with gastric function may modify the course of infantile pellagra and other diseases, the importance of this organ in the maintenance of normal water metabolism and the role of gastric dysfunction in the production of edema cannot be overlooked.

From the foregoing it is apparent that there is an intimate interrelationship between the stomach, the liver and the kidney in the maintenance of normal water metabolism. The fact that edema is a much more constant feature in infants than in adults suffering from pellagra implies that the mechanism regulating water metabolism is more sensitive in children than in adults. McCarrison [33] has shown that young animals are much more liable to edema when malnourished than adults on the same diet. In this connection it is noteworthy that it is much more difficult to induce damage to the liver with mealie pap and sour milk in old than in young rats,[34] and our aspiration biopsy studies of pellagrins have revealed a notable difference in the nature and severity of the pathologic process in the livers of adults as compared with those of children.[35]

Another feature of infantile pellagra is the frequent occurrence of steatorrhea. The appearance of large quantities of split and unsplit fat in the stools is common to a number of other diseases. The factors responsible for steatorrhea are still unsettled.

In a series of excellent reviews Parsons has repeatedly emphasized that "the probable explanation of celiac disease lies in a change of physico-chemical nature in the absorptive mechanism of the intestine." [18a] This view has recently been reaffirmed both for celiac disease and for sprue.[36] The flat blood fat curves repeatedly recorded for patients with these diseases [37] may, in our opinion, be as easily accounted for by an increased tolerance for fat as by a deficient absorption of it. Moreover, the fat balance curves published by Parsons [18a] indicate that patients suffering from celiac disease are capable of absorbing considerable amounts of fat. However, both in celiac disease and in sprue signs of vitamin deficiency as well as edema frequently become manifest. Tetany, commonly observed in celiac disease, has also been described by Drewe in malnourished African children suffering from steatorrhea.[38] Parsons concluded that whether or not the disease is initiated by avitaminosis "there can be no shadow of doubt that a defect, not in supply, but in the absorption of vitamins resulting from the impaired alimentary absorption is the cause of many of the most characteristic symptoms of the disorder."

Blackfan and Wolbach [39] have described the occurrence in children of fatty livers and cystic fibrosis of the pancreas in association with evidence of vitamin A deficiency. Later Andersen reported similar changes in infants and children.[13] She emphasized the invariable association of cystic fibrosis of the pancreas and was undecided as to whether the primary cause of the steatorrhea was a vitamin deficiency or the pancreatic lesions.

Judging from clinical and experimental evidence, we are of the opinion that steatorrhea can be initiated by a dietary imbalance and is not necessarily due to a disturbance in absorption of fat. Experimentally we have demonstrated that rats fed on mealie pap and sour milk commonly have cystic changes of the pancreas similar to those described and portrayed by Andersen in children.[13] In our dietary experiments the rats also were found to have fatty livers.[34a] Whereas Andersen was unable in her human subjects to ascertain the sequential relations between the fatty liver and the pancreatic lesion, we can state with assurance [34b] that in rats the fatty liver precedes by many months the cystic changes in the pancreas.[40]

Clinically there seems little doubt that infantile pellagra is directly attributable to malnutrition. From our careful analysis of the diets of our patients, as well as those reported in Trowell's series, it is clear that the fat content of the diets is extremely low and is insufficient to account for the large quantities of fat excreted in the feces. In these circumstances the steatorrhea in infantile pellagra can be accounted for only by an increased excretion of fat. In a

33. McCarrison, R.: Studies in Deficiency Disease, London, H. Frowde, 1921.

34. (*a*) Gillman, J.; Gillman, T.; Gilbert, C., and Mandelstam, J.: The Production of Severe Hepatic Injury in Rats by Prolonged Feeding of Maize-Meal Porridge (Mealie-Pap) and Sour Milk, to be published. (*b*) Gilbert, C., and Gillman, J.: Diet and Disease in the Bantu, Science **99**:398 (May 19) 1944.

35. Gillman, J., and Gillman, T.: Liver in Pellagra, Lancet **2**:161 (July 29) 1944; footnote 2.

36. Stannus, H. S.: Sprue, Tr. Roy. Soc. Trop. Med. & Hyg. **36**:123 (Nov.) 1942.

37. Parsons.[18a] Adlersberg, D., and Sobotka, H.: Fat and Vitamin A Absorption in Sprue and Jejunoileitis, Gastroenterology **1**:357 (April) 1943.

38. Drewe, F.: Personal communication to the authors.

39. Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants: A Clinical and Pathological Study, J. Pediat. **3**:679 (Nov.) 1933.

40. In a single fatal case of severe malnutrition recently observed, the pancreas showed the early development of cystic changes such as we have seen in our rats. The liver in this patient was grossly fatty.

previous study[2] we have suggested that the accumulation of fat in the liver and its excretion in the stool, associated with extreme emaciation, are an expression of the conversion of carbohydrate into fat together with an inability of the tissues to utilize this fat.

Thus, although infantile pellagra is initiated by a dietary imbalance, once the disease has progressed to the stage where the fatty liver, steatorrhea, edema and dermatitis become manifest, then vitamins fail to improve the conditions of a large proportion of the patients. The failure of vitamins, even when administered parenterally, indicates that the factor of absorption is unimportant. The organism is apparently incapable of utilizing vitamins even when made available in large concentrations by parenteral routes. But, even when vitamins are said not to be absorbed from the alimentary tract, powdered stomach administered orally is able within two to three days to produce such a profound readjustment in the metabolism of the diseased organism that the diet and vitamins can be effectively utilized.

Whereas in infantile pellagra dietary imbalances lead to the development of steatorrhea, this steatorrhea in infantile pellagra, as in celiac disease, may in turn be responsible for an intensification of the severity of the disease, as expressed by disturbed gastric function, macrocytic anemia and edema. This intensification of the clinical picture is probably attributable not so much to the malabsorption of essential dietary factors as to the hitherto unappreciated subtle changes produced by the continuous presence of fat in the alimentary tract.

It has been known for a long time that neutral fat inhibits gastric secretion as well as gastric motility. This inhibition results from the contact of neutral fat with the mucous membrane of the duodenum, jejunum and large bowel. By a series of carefully planned experiments[41] a hormone (enterogastrone) said to be responsible for the inhibition of gastric function resulting from the ingestion of fat was isolated. It is not inconceivable that the continuous presence of fat in the alimentary tract in infantile pellagra may lead to the liberation of enterogastrone. This hormone, in turn, contributes to the partial or complete suppression of gastric function. We have already indicated that the stomach, together with the liver and the kidney, is intimately concerned with water metabolism. Any interference with this delicate mechanism might result in the production of edema.

It is generally known that the stomach, through its intrinsic factor, influences hemopoiesis. The chronic inhibition of gastric function by the continuous liberation of enterogastrone in steatorrhea might so disturb the gastrohepatic relationship as to lead to the macrocytic or microcytic anemia so frequently observed in infantile pellagra.[9] Moreover, the apathy, atonia and anorexia, manifestations of severe malnutrition, can also be explained by an impairment of gastric function.

Distention of the bowel is known to produce profound effects on hepatic function.[42] The pronounced distention of the intestinal tract in steatorrheas cannot be overlooked in the light of its possibly deleterious effects on the functions of the liver.

That infantile pellagrins do not respond to vitamins but respond dramatically to powdered stomach strongly suggests that the latter preparation supplies an essential substance normally elaborated by the stomach, which breaks the vicious circle, facilitating in this way the recovery of the patient.

The similarities between infantile pellagra and other conditions in which steatorrhea, edema, cutaneous lesions, anemia, anorexia and fatty changes in the liver occur suggest a disturbance in the same underlying mechanism. Whether the initiating factor is the same in all these diseases remains to be determined. Nevertheless, during their evolution a disturbance of fat metabolism eventually occurs. Once this disturbance becomes manifest, all these diseases seem to follow a common course in their subsequent evolution.

The stages in the emergence of the signs and symptoms associated with sprue have been graphically described by Manson-Bahr. Dyspepsia, followed by the typical gastrointestinal disturbances, precedes by months the onset of the anemia.[21] As in infantile pellagra, so in

41. Feng, T. P.; Hou, H. C., and Lim, R. K. S.: Mechanism of the Inhibition of Gastric Secretion by Fat, Chinese J. Physiol. **3**:371 (Oct.) 1929. Kosaka, T.; Lim, R. K. S.; Ling, S. M., and Liu, A. C.: On the Mechanism of the Inhibition of Gastric Secretion by Fat: A Gastric-Inhibitory Agent Obtained from the Intestinal Mucosa, ibid. **6**:107 (Feb. 15) 1932. Ivy, A. C., and Gray, J. S.: Enterogastrone, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, p. 405. Babkin, B. P.: Secretory Mechanism of the Digestive Glands, New York, Paul B. Hoeber, Inc., 1944.

42. Schnedorf, J. G., and Orr, T. G.: The Effect of Small Intestine Distention upon the Bile and Urine Flow: Its Possible Relationship to the Hepato-Renal Syndrome, Am. J. Digest. Dis. **8**:303 (Aug.) 1941.

sprue, the presence of fat in the intestine probably induces the formation of enterogastrone, which in turn inhibits gastric activity. Judging from the length of time by which the steatorrhea precedes the onset of the anemia in sprue, the inhibition of gastric function probably continues for several months.

Castle and others,[43] from their thorough study of sprue, concluded that the macrocytic anemia in this disease is attributable to the inhibition of the formation of the intrinsic factor. However, Molina demonstrated the presence of free hydrochloric acid in 82 of 100 patients with sprue examined. If, as we have suggested, enterogastrone is responsible for the inhibition of the function of the stomach in steatorrhea, it would appear at first difficult to account for the dissociation of the activities of the gastric mucosa.

The stomach is known to have at least three different types of function; they are the formation of gastric juice, the production of the intrinsic factor and the excretion of various substances, including injected neutral red. There can be dissociation of the secretory activities of the stomach.[44] In cases of pellagra, for example, free acid may continue to be formed even though the stomach is unable to excrete neutral red, and vice versa. Moreover, in a single classic case of tropical sprue Dr. Foy and Dr. Kondi kindly afforded us the opportunity of testing the excretory function of the stomach with neutral red. The macrocytic anemia in this patient, on the basis of Castle's finding, was strong evidence of an impairment in the formation of the intrinsic factor. The excretory function of the stomach was also impaired, but free acid was secreted after histamine had been injected. Thus in this case the secretion of free acid was not grossly impaired, but there was a delay in the excretion of neutral red, and the intrinsic factor was lacking. It is not unlikely, therefore, that enterogastrone may cause a differential inhibition of gastric function resulting in suppression either of the formation of the intrinsic factor as in sprue or of the secretion of hydrochloric acid as in some cases of pellagra. Prolonged inhibition, as in chronic sprue, may eventually result in complete suppression of all the functional activities of the stomach. Once the steatorrhea is fully established, the disease changes its character, and then the edema, emaciation, anorexia and fatty liver develop as in infantile pellagra.

Since this analysis of the evolution of sprue and infantile pellagra is applicable to other diseases in which steatorrhea is a dominating feature, and in view of the beneficial but not entirely satisfactory results achieved with crude liver extracts, it is justifiable to suggest that powdered stomach, so successful in infantile pellagra, be substituted for or administered with crude liver extract in the treatment of steatorrhea.

Despite the close relationship known to exist between the stomach and the liver, it is interesting that much greater importance should have been attached to liver extracts than to the principles isolated from the stomach only three years later. Powdered stomach has a remarkable lipotropic effect on the liver, restores the gastrohepatorenal relationship (as evidenced by the removal of the edema), benefits the nervous and hemopoietic systems in anemias and facilitates the utilization of essential food substances with consequent suppression of steatorrhea in a severely damaged organism. All these important effects indicate the necessity for an assessment of the active principles of the stomach and of their relation to the active principles of the liver in the bodily functions connected with steatorrhea.

Finally, a significant thesis emerges from this and other of our studies: namely, that a disease at a certain stage loses its connection with the initial cause. The subsequent course of the disease may then be determined by the secondary pathologic changes. Once the disease manifests its altered character, our efforts to break the vicious spiral should then be directed toward the mainspring responsible for maintaining the disease process and for interfering with the harmonious integration of bodily activities. This approach may stimulate and direct the search for new forms of therapy for those diseases which hitherto have proved refractory to the present methods of treatment.

SUMMARY

From a study of 23 cases of pellagra in infants and children it was demonstrated that the main clinical findings were a varying degree of edema, dermatitis, angular and labial stomatitis (cheilosis), graying of the hair with varying degrees of alopecia, steatorrhea and a large fatty liver.

43. Castle, W. B., and others: Etiology and Treatment of Sprue, Arch. Int. Med. **56**:627 (Oct.) 1935.

44. Gillman, T.: Excretion of Neutral Red by the Gastric Mucosa; A Valuable Test of Gastric Function, South African J. M. Sc. **8**:50 (Feb.) 1943; footnote 32*c*. Solovey, E. G.: Excretory Function of the Stomach, Dissert., Moscow, 1938; cited by Lourja, R. A.: The Excretory Function of the Stomach and Its Clinical Role, Acta med. U. R. S. S. **2**:310, 1939.

Histologic examination of fragments of liver obtained by aspiration biopsy on the day of the patient's admission revealed the presence of a greater or lesser amount of fat in the liver cells. The fatty change in the liver was found to be a constant feature of infantile pellagra, and it was not due to intercurrent infection as was previously believed. The degree of accumulation of fat in the liver proved to be a much more accurate measure for predicting the outcome of each case than the clinical findings. No aspiration biopsies were essential in controlling therapy, for it was found that in cases with great accumulation of fat in the liver vitamins together with a full diet appeared to aggravate the condition. All the patients in this series treated with vitamins died. Liver extract and especially powdered stomach depleted the fat from the liver, and this depletion in turn was invariably associated with a dramatic improvement in the condition of the patient.

Powdered stomach has a vigorous lipotropic action in infantile pellagra. Five days' treatment with 10 Gm. a day was adequate to allow for a continued depletion of fat from the liver even after treatment was suspended. A study of the reactions of the liver during therapy with vitamins, liver extract and powdered stomach led to the conclusion that, although infantile pellagra is initiated by dietary imbalance, the secondary pathologic changes which supervene cannot be alleviated by a full diet and vitamin concentrates.

The edema of infantile pellagra is not related to the level of the serum proteins. It was suggested that, at least in infants, the normal water metabolism is dependent on a subtle but intimate interrelationship of the stomach, liver and kidneys. The edema in infantile pellagra probably results from a disturbance of this gastrohepatorenal mechanism.

In view of the low fat content of the diet, the steatorrhea in infantile pellagrins was regarded as resulting not from malabsorption of fat but rather from an increased excretion of fat into the bowel. It was concluded that in infantile pellagra carbohydrate is converted into fat which cannot be utilized. The evidence available indicates that fat continuously present in the bowel liberates enterogastrone, which in turn inhibits gastric function. It is suggested that this chronic inhibition of gastric function with the consequent disturbance in the gastrohepatic relationship could lead to the macrocytic or microcytic anemia, nervous symptoms and edema so commonly associated with steatorrhea.

The similarities between infantile pellagra and other conditions in which steatorrhea appears early in the disease process strongly suggest that once the disturbance in fat metabolism has occurred, irrespective of the initiating cause, all these diseases follow a common course in their later evolution.

In view of the rapid cessation of the steatorrhea and the accompanying general improvement in infantile pellagrins treated with powdered stomach, it is recommended that this treatment be given universal trial for other diseases in which steatorrhea is a prominent feature.

Prof. Raymond A. Dart gave suggestions for this study. Miss Winifred Till and Mr. Sidney Dry gave technical assistance.

COLD HEMAGGLUTINATION IN PRIMARY ATYPICAL PNEUMONIA AND OTHER COMMON INFECTIONS

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AND
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Recent reports indicate that large amounts of a cold hemagglutinin appear frequently in the blood of patients with primary atypical pneumonia.[1] Apparently, this is not true of patients with other common infections of the respiratory tract, such as pneumococcic pneumonia, the common cold, influenza and pulmonary tuberculosis.[2] In view of the simplicity of the titration of cold agglutinin in the serum, this procedure promises to be of value as a practical aid in the differentiation of primary atypical pneumonia from the other common types of pneumonia. This differentiation is often difficult, since no clinical or laboratory finding is characteristic of the former syndrome.[3]

During the winter and spring of 1943-1944, we studied the phemonemon of cold hemagglutination in 115 patients with pneumonia, in 257 patients with other infections and in 100 normal hospital personnel. This was done to evaluate further the specificity and significance of high titers of cold agglutinin in persons with primary atypical pneumonia and to determine whether this serologic test is of any use in the detection of the carrier state and of certain minor infections of the respiratory tract with the agent (or agents) causing this syndrome. The following is a report of our observations on the 472 subjects studied.

NATURE OF COLD HEMAGGLUTINATION

The phenomenon of cold hemagglutination dealt with in this study is due to the action of "a non-specific agglutinin capable of producing clumping of human erythrocytes, irrespective of blood group and usually of certain other heterologous erythrocytes."[4] Although activity is greatest at 0 to 5 C. and disappears at 37 C., the range of temperature in which hemagglutination occurs seems to widen as the concentration of the agglutinin increases. Apparently, the erythrocytes used in the demonstration of this phenomenon are of fundamental importance, since irregular variations occur in the agglutinability of cells of the various homologous blood groups and of heterologous red blood cells (i. e. rabbit, sheep, etc.).[1b]

Cold hemagglutinin has been commonly found in normal serums and has been detected in large amounts in serums of persons with a great variety of diseases, particularly trypanosomiasis, hematologic disorders, hepatic cirrhosis and, as already indicated, primary atypical pneumonia.[5] The general significance of its presence is unknown. There is some evidence that cold hemagglutinin is an immune body, closely related to serum globulin. For a detailed review of the general subject of cold hemagglutination, the recent article by Stats and Wassermann should be consulted.[5]

METHODS

Titrations of the cold hemagglutinin content of the specimens of serum were carried out by the following method: Five cubic centimeters of blood was obtained by venipuncture with use of dry syringe and placed in a clean dry test tube. The clot was separated at room temperature by rimming, and the sample was

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1. (*a*) Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinins (Auto-Hemagglutinins) in Primary Atypical Pneumonias, Science **97**:167, 1943. (*b*) Turner, J. C.; Nisnewitz, S.; Jackson, E. B., and Berney, R.: Relation of Cold Agglutinins to Atypical Pneumonia, Lancet **1**:765, 1943. (*c*) Horstmann, D. M., and Tatlock, H.: Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, J. A. M. A. **122**:369 (June 5) 1943. (*d*) Meiklejohn, G.: The Cold Agglutination Test in the Diagnosis of Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **54**:181, 1943.

2. Siffert, R. S., and Krautman, B.: Cold Hemagglutination Reactions in Tuberculosis, J. Lab. & Clin. Med. **29**:270, 1944. Turner and others.[1b] Horstmann and Tatlock.[1c] Meiklejohn.[1d]

3. Dingle, J. H., and Finland, M.: Virus Pneumonias: II. Primary Atypical Pneumonias of Unknown Etiology, New England J. Med. **227**:378, 1942.

4. Wiener, A. S.: Blood Groups and Transfusion, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1939, p. 35.

5. Stats, D., and Wassermann, L. R.: Cold Hemagglutination—An Interpretative Review, Medicine **22**: 363, 1943.

centrifuged for about ten minutes. The serum was pipetted off into a clean test tube. After serum had been taken for the test, the remainder was stored without preservative at 5 C. No serum was stored in the refrigerator unless it had been removed from the clot, since absorption of hemagglutinin occurs at low temperatures.

Serial dilutions were made of 0.1 cc. of the serum in isotonic solution of sodium chloride in small test tubes. The 0.1 cc. of serum was added to 0.9 cc. of saline solution in the first tube, and 0.5 cc. of the resultant mixture was added to 0.5 cc. of isotonic saline solution in the second tube and so on. A tube containing only 0.5 cc. of saline solution was kept as a control. To each 0.5 cc. of the diluted serum and to the control, 0.2 cc. of a 2 per cent suspension of thrice washed group O erythrocytes was added, making final dilutions of 1:14, 1:28, 1:56, etc. The tubes were then shaken and refrigerated at 5 C. for sixteen to twenty hours.

To eliminate unnecessarily long series of dilutions with serums containing little or no cold agglutinin, a test consisting of three dilutions (1:14, 1:28, 1:56) was set up first. If the titer reached 1:56, a second series of dilutions, from 1:14 to 1:3,584, was set up. Titers in excess of 1:3,584 were determined with a third series of dilutions.

The end point of the titration was the highest dilution in which hemagglutination was detectable microscopically after vigorous shaking to resuspend the sedimented erythrocytes. After the last dilution in which macroscopic agglutination was apparent had been noted, the cells in subsequent tubes were observed directly with the low power objective of the microscope, daylight being used as the source of illumination. At the end point, only a slight amount of hemagglutination was present, as indicated by occasional aggregates of 3 to 5 erythrocytes. In the absence of macroscopic clumping, successive tubes were examined microscopically until a perfectly smooth suspension of red cells was apparent. The control suspension of red blood cells in isotonic solution of sodium chloride failed to reveal agglutinated (or adherent) red blood cells under the described conditions.

The readings were performed quickly at room temperature. Moisture condensing on the cold test tubes was removed by wiping with a clean towel. If cold agglutination was observed, the cell suspensions were incubated at 37 C. for one to two hours to allow the disappearance of the agglutination, in order to exclude agglutinins active at this temperature.

A high titer of cold agglutinin was indicated by the formation of solid disks of cells in the low dilutions. Such disks were fragmented into coarse clumps by shaking. With moderately increased titers, the disks were easily broken up into finely granular clumps. Low titers (up to 1:28) were often discernible only with the aid of a concave mirror or with the microscope.

Using this method, we found that the end point of the titration varied with the magnification used in reading it and with the time of refrigeration (table 1). Microscopic agglutination was usually present in one or two dilutions higher than the last one in which it was detectable grossly. Moreover, readings at the end of three hours were one or two dilutions lower than those obtained in sixteen to twenty hours. Apparently the prolonged periods of sedimentation of the cells in the cold increased their tendency to agglutinate (table 1). It will be noted in the presentation of our results that the titers of cold hemagglutinin obtained by us in normal controls and in patients with certain infectious diseases are somewhat higher than those reported elsewhere.[6] It is our belief that these differences are in all likelihood due to variations in method.

The 2 per cent suspension of human group O cells was prepared about every forty-eight hours from citrated blood obtained from a small group of donors and stored at 5 C. The suspensions were made from a stock sample of blood kept at 5 C. for periods up to four days. This precaution was taken because of the reported observation that red cells exposed to saline solution rapidly lose their agglutinability while those in contact with plasma do not.[5] However, we were unable to detect any significant alteration in the agglutinability of suspensions of red cells used as long as

TABLE 1.—*Effects of Magnification and Refrigeration Time on the End Points of Cold Agglutinin Titrations of Human Serum*

	Refrigeration for 3 Hours		Refrigeration for 20 Hours	
Serum	Macroscopic	Microscopic	Macroscopic	Microscopic
1	1:224	1:448	1:448	1:1792
2	1:56	1:112	1:112	1:448
3	0	1:14	0	1:14
4	1:56	1:112	1:112	1:448
5	0	1:28	0	1:28
6	1:14	1:56	1:28	1:112
7	1:112	1:448	1:224	1:896
8	0	0	1:14	1:28
9	1:14	1:28	1:28	1:112
10	0	1:28	1:14	1:56
11	0	0	0	0
12	0	0	0	0

ninety-six hours after preparation. The blood used in preparing the suspensions was warmed to room temperature, and the cells were washed three times in 10 volumes of isotonic solution of sodium chloride.

In this study, no attempt was made to detect cold agglutinins in dilutions below 1:14. No effort was made to note the agglutinability of the subject's own cells by his serum in the cold (autoagglutination).

MATERIAL

The normal subjects were hospital personnel who came into contact with patients while working in the hospital wards. Each was questioned prior to the test concerning the occurrence of a recent acute infection of the upper respiratory tract or other illness (within six months), especially pneumonia, chronic cough, mumps, measles, scarlet fever, malaria or jaundice. It was assumed that some of these persons had been exposed to primary atypical pneumonia, since the disease was a common one in the hospital and was encountered from time to time in the hospital personnel. Only 1 titration was done for each normal subject.

The clinical and laboratory data for the patients studied were reviewed, and those for whom the diagnoses were reasonably well established were included in the series (table 2).

A diagnosis of primary atypical pneumonia seemed warranted for 91, or 79 per cent, of 115 patients with pneumonia. In selecting this group, we were guided by

6. Footnotes 2 and 4.

the diagnostic criteria outlined in recent articles,[7] particularly the mode of onset, the clinical course, the results of physical examination, the roentgenographic findings, the results of culture of sputum when done and the type of responses to sulfonamide drugs when given. Since none of these criteria are specific, differential diagnosis was often difficult.

In the 24 other patients with pneumonia, the disease seemed to be of bacterial origin. There were 8 with lobar pneumonia or bronchopneumonia due to pneumococci (types 1, 2, 4, 5, 7, 12); in 1 the disease was attributed to the beta hemolytic Streptococcus and in 1 to Staphylococcus aureus. For 14 others, although no pathogenic bacteria were found in the sputum, the findings suggested lobar pneumonia or bronchopneumonia caused by bacteria. In 5 of these 24 patients, the disease was complicated by empyema or pleural effusion.

On the other hand, in several cases of primary atypical pneumonia in which streptococci (alpha or beta hemolytic) were found in the sputum, the organisms were regarded as the usual flora seen in the throats of the many normal persons.[7a] However, in some of these cases, these organisms may have acted as secondary invaders as reported by Longcope[7b] and Thomas.[8]

For the patients with pneumonia the titration of hemagglutinins was usually done shortly after their admission to the hospital and at weekly intervals thereafter. For a few of them, we were able to follow the titer for as long as two to three months.

For persons with other infectious diseases, many of the determinations of cold agglutinin were single observations made at varying times after the onset of the disease. In some instances, especially for patients with measles and scarlet fever, determinations were made at the height of the disease and two or three weeks later.

The group classified as having minor infections of the respiratory tract included patients with acute catarrhal fever, acute pharyngitis, acute tonsillitis, influenza and acute tracheobronchitis. Infections of this type have been observed during epidemics of primary atypical pneumonia.[7c] The patients with a diagnosis of influenza were seen during an epidemic caused by type A influenza virus in December 1943 and January 1944. In general, the illnesses in this group were of short duration, and repeated observations of the cold hemagglutinin titer during convalescence were not often possible. However, the late influence of such illnesses on the cold hemagglutinin titer was studied in some of the normal hospital personnel, as indicated subsequently.

TABLE 2.—*Distribution of Cold Hemagglutinin Titers in 472 Subjects*

Clinical Group	Subjects	Tests	Cold Hemagglutinin Titers: 0	1:14	1:28	1:56	1:112	1:224	1:448	1:896	1:1792	1:3584	1:7168	1:14000
Normal controls	100	100	34	17	27	11	8	3	..	..	..	..	..	..
Primary atypical pneumonia	91	254	11	8	8	8	10	6	5	13	7	13	1	1
Bacterial pneumonias (total)	24	91	5	5	5	3	2	4	..	..	..	..	..	..
Pneumococcic pneumonia	8	25	3	..	2	2	..	1	..	..	..	..	..	..
Pulmonary tuberculosis	4	8	2	..	1	..	..	1	..	..	..	..	..	..
Minor infections of respiratory tract	46	50	26	6	4	4	3	3	..	..	..	..	..	..
Measles	24	36	3	4	5	4	4	2	1	1	..	..	..	..
Rubella	9	9	3	1	3	1	1	..	..	..	..	..	..	..
Mumps	37	40	17	10	4	6	..	..	..	..	..	..	..	..
Mumps orchitis	18	20	..	3	5	4	3	1	..	1	..	1	..	..
Mumps encephalitis	2	2	..	..	..	1	1	..	..	..	..	..	..	..
Chickenpox	6	6	..	2	..	2	2	..	..	..	..	..	..	..
Acute catarrhal jaundice	14	16	6	3	3	1	1	..	..	..	..	..	..	..
Infectious mononucleosis	7	15	..	..	..	1	..	1	..	3	1	1	..	..
Scarlet fever	26	39	6	2	3	4	5	3	1	1	1	..	..	..
Rheumatic fever	22	30	7	7	4	..	1	2	..	1	..	..	..	..
Gonorrhea	23	23	5	4	7	4	2	1	..	..	..	..	..	..
Seropositive syphilis	8	8	4	1	1	2	..	..	..	..	..	..	..	..
Filariasis	8	8	4	2	1	1	..	..	..	..	..	..	..	..
Amebiasis	2	2	1	1	..	..	..	..	..	..	..	..	..	..
Coccidiomycosis	1	1	..	1	..	..	..	..	..	..	..	..	..	..
Total	472	758	134	77	81	57	43	27	7	20	9	15	1	1

The cases of infectious mononucleosis were typical, as indicated by generalized lymphadenopathy, splenomegaly, lymphocytosis and the presence of "lymphoid" cells in the blood and the frequent finding of large amounts of sheep cell agglutinins in the serum. Fourteen jaundiced patients were considered to have acute catarrhal jaundice.

RESULTS

The results of titrations of the serum for cold hemagglutinin in 472 subjects are presented in table 2 and chart 1. To make the various clinical groups studied more nearly comparable, only the initial titers obtained for patients with primary atypical pneumonia are compared with the highest values for the patients with other infections whenever more than one determination was made.

With this method, a cold hemagglutinin was detected in 338 serums (71.6 per cent). It is likely that the number would have been greater if titers below 1 : 14 were determined. The high-

7. (*a*) Kneeland, Y., and Smetana, H.: Current Bronchopneumonia of Unusual Character and Unknown Etiology, Bull. Johns Hopkins Hosp. **67**:229, 1940. (*b*) Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X): A Report of Thirty-Two Cases with Two Deaths, ibid. **67**:268, 1940. (*c*) Dingle, J. H.; Abernathy, T. J.; Barger, G. F.; Buddingh, G. H.; Feller, A. E.; Langmuir, A. R.; Ruegsegger, J. M., and Wood, W. B.: Primary Atypical Pneumonia, Etiology Unknown, War Med. **3**:223 (March) 1943. (*d*) Drew, W. R. M.; Samuel, E., and Ball, M.: Primary Atypical Pneumonia, Lancet **1**:761, 1943. (*e*) Dingle and Finland.[8]

8. Thomas, H.: The Role of Alpha Hemolytic Streptococcus in Pneumonia, Bull. Johns Hopkins Hosp. **72**:218, 1943.

est values (above 1:224) were obtained with greatest frequency in patients with primary atypical pneumonia and infectious mononucleosis. Similar values were also occasionally obtained for patients with measles, mumps orchitis, scarlet fever and rheumatic fever but not for normal controls and for patients with the other infectious diseases studied.

Normal Controls.—A cold hemagglutinin was found in 66 per cent of 100 serums obtained from normal hospital personnel. The titer varied from 0 to 1:56 in 89 per cent, and in half of the serums it was 1:14 or less. In 11 per cent it ran out to 1:112 or 1:224 (table 2).

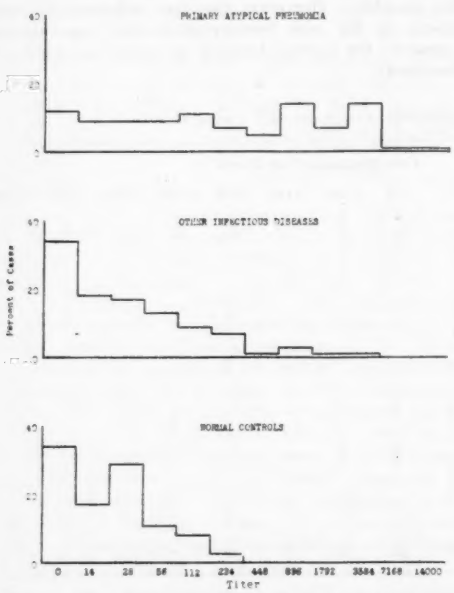
PRIMARY ATYPICAL PNEUMONIA
OTHER INFECTIOUS DISEASES
Percent of Cases
NORMAL CONTROLS
0 14 28 56 112 224 448 896 1792 3584 7168 14000
Titer

Chart 1.—Percentage distribution of cold hemagglutinin titers of patients with primary atypical pneumonia, of patients with other infectious diseases and of normal controls.

Since an increased titer of cold hemagglutinin may be present for months after the recovery from primary atypical pneumonia and perhaps other infectious diseases as well, an attempt was made to determine whether the higher values in this group (1:112 and 1:224) were related to the recovery from a recent illness. Accordingly, the controls were divided into two groups on the basis of their histories, and the titers in each group were compared (table 3). Since all the controls were white persons, racial influences did not have to be taken into account. The relation of the various blood groups to the titer was not determined.

Of 38 controls who stated that they had had no colds, cough, sore throats or any known illnesses for about six months, the cold hemagglutinin titer varied from 0 to 1:56 in 36 (93 per cent) and reached 1:112 in 2 persons. A comparison of the range of titer in men and in women revealed that titers of 1:56 or 1:112 occurred in 3 of 10 women and of 1:56 in 2 of 28 men. Although the numbers of subjects are small, it is possible that the distribution of the highest values in this subgroup of the normal controls was determined by sexual differences.

In 62 controls with histories of a recent acute infection of the respiratory tract or other infectious disease within a period of about six months, the titer exceeded 1:56 in 9 and ran out to 1:224 in 3. Although this group consisted of 9 women and 53 men, the highest titers occurred only in the men. They were found in 3 of 25 subjects with a history of a recent cough, in 2 of 8 with a history of sore throat, in 2 of 14 who had had a recent cold and in 2 subjects who had recently recovered from measles. A calculation of the statistical significance of the difference in the incidence of titers above 1:56 between the two groups (by the method of chi square and with use of a probability of 0.05 as the limit of significance) indicated that a titer of 1:56 was probably related to a history of a recent infectious disease.

TABLE 3.—*Relation of Cold Hemagglutinin Titer to a History of Recent Illness in Normal Controls*

Group of Normal Controls	Number	Cold Hemagglutinin Titers					
		0	1:14	1:28	1:56	1:112	1:224
No history of recent illness	38	21	4	8	3	2	0
History of recent illness..	62	13	13	19	8	6	3

Primary Atypical Pneumonia.—Of the 91 persons with primary atypical pneumonia, a cold hemagglutinin was detected in the serum on the initial examination in 80 (85.7 per cent). In 40 (44.9 per cent) the titer was greater than the highest value (1:224) seen in normal controls, and in 56 (61 per cent) it exceeded 1:56, the highest titer in 89 per cent of the controls. In 35 patients (38 per cent) the initial titer ran out to 1:896 or beyond. Values of 1:3,584 or more were obtained in 15 (16 per cent). The highest titers of cold agglutinin (1:7,168 and 1:14,000) encountered in the entire group of 472 subjects were obtained in the serums of persons with primary atypical pneumonia. On repetition of the titrations in the course of the syndrome, values above 1:56 occurred in 73 patients (80.2 per cent) and above 1:224 in 54 (59 per cent) (table 4).

On the other hand, in 18 patients (19.7 per cent) the highest cold agglutinin values did not exceed the dilution of 1:56, and in 19 others (20 per cent) the titer ranged from 1:112 to 1:224. In some cases these lower values could be attributed to a too short period of observation (see "Relation of Cold Hemagglutinin Titer to Other Features of Primary Atypical Pneumonia"); in others it may have been due to mistakes in diagnosis. However, in 16 persons with primary atypical pneumonia, despite a sufficiently long period of observation during which repeated tests were run, a rise in cold agglutinin titer failed either to occur or to reach the levels obtained for most of the patients (table 8).

TABLE 4.—*Initial and Highest Cold Hemagglutinin Titers of 91 Patients with Primary Aypical Pneumonia*

Titer	Initial	Highest
0	11	5
14	8	4
28	8	5
56	8	4
112	10	13
224	6	6
448	5	8
896	13	12
1792	7	12
3584	13	15
7168	1	4
14000	1	3
Total	91	91

While the range of titer in this group of 37 patients with the lowest titers was similar to that for normal controls (0 to 1:224), the incidence of titers above 1:56 on the initial examination was much greater (43 per cent as compared with 11 per cent for normal controls).

Bacterial Pneumonia.—In the 24 patients with bacterial pneumonia, a cold hemagglutinin when found was present in low titer, despite repeated tests during prolonged periods of observation (in persons with pneumococcic pneumonia for periods of eight to thirty-two days after the probable onset and in persons with the other bacterial pneumonias for periods of eight to ninety-three days). In the 8 patients with pneumococcic pneumonia the highest values were usually below 1:112. In 1 person, in whom the titer rose to 1:224 during convalescence, the sputum contained a type 12 pneumococcus and the roentgenologic findings and the course resembled those of many persons with primary atypical pneumonia. In 5 of the other 16 patients, the titer reached 1:112, or 1:224. In 4 of these 5 patients an empyema or pleural effusion developed, and in 3 the highest titer (1:112 or 1:224) was not apparent for fourteen to thirty-two days after the probable onset.

In summary, a comparison of the cold hemagglutinin titers in 91 patients with primary atypical pneumonia and in 24 with bacterial pneumonia shows that large amounts of cold hemagglutinin were present in the serum only in those with the former syndrome. In persons with uncomplicated pneumococcic pneumonia the cold agglutinin titers were usually low (0 to 1:56). In persons with bacterial pneumonia complicated by empyema and pleural effusion, the cold hemagglutinin values were observed to rise to 1:112 and 1:224 during the course of the disease in most instances. On the other hand, maximum titers of 1:224 or less were obtained also in 40 per cent of the persons with primary atypical pneumonia. Although for these patients this serologic test was not distinctive, titers of 1:112 and 1:224 were more common in patients with primary atypical pneumonia than in patients with bacterial pneumonia and in normal controls.

Other Infections.—Of 257 patients with miscellaneous common infections exclusive of pneumonia, a cold hemagglutinin was detected in the serums of 173 (67.3 per cent). The titers exceeded 1:56 in 50 (19.4 per cent) and ran out beyond 1:224 in 13 (5.0 per cent). High titers comparable to those observed in the serums of persons with primary atypical pneumonia were frequently encountered in persons with infectious mononucleosis (table 5) and occasionally in patients with mumps orchitis, measles, scarlet fever and acute rheumatic fever.

TABLE 5.—*Laboratory Data for Patients with Infectious Mononucleosis*

Case No.	Titer: Cold Agglutinin	Titer: Hetrophile Antibody	White Blood Cell Count: Total	Poly.	Lym.	Eosin.	Mono.	Baso.	Lymphoid.
1	1:3,584	1:1,792	8,500	12	84	2	2	0	+
2	1:224	1:448	14,500	14	80	2	4	0	+
3	1:56	1:1,792	20,000	21	76	0	3	0	+
4	1:1,792	1:14,000	7,500	12	88	0	0	0	+
5	1:896	1:3,584	8,600	23	77	0	0	0	+
6	1:896	1:112	5,350	46	51	1	2	0	+
7	1:896	1:28	5,600	42	50	6	2	0	+

In the subgroup of patients with the 5 infectious diseases mentioned (97 patients) in which the highest titers were observed the cold hemagglutinin titer exceeded 1:56 in 38 and 1:224 in 9. In this group, the incidence of titers above 1:56 was greater than in the group with other infections, in which the titer never exceeded 1:224. The statistical significance of this difference, however, was open to question on the basis of our data, since the tests were often repeated on the patients in the former group and not on those in the latter. On the other hand, it

is not unlikely that the incidence of serums containing cold hemagglutinin in patients with these 5 diseases and the height of the titers would approach the values for patients with primary atypical pneumonia if the numbers of patients with each disease studied and of titrations were similar.

In the patients with infectious diseases (160) in whom the titer did not exceed 1 : 224, including those with minor infections of the respiratory tract, the titer exceeded 1 :56 in 15. This figure was not significantly different from that for the incidence of such titers in normal controls. Of 46 patients with minor infections of the respiratory tract, titers above 1 : 56 occurred for 6. This figure was similar to that obtained for the 62 normal controls (14 per cent), many of whom gave a history of a recent infection of this type.

To summarize, the appearance of large amounts of cold hemagglutinin in the serum is not specific for primary atypical pneumonia among infectious diseases but may occur in certain other infections. These high titers, however, were limited to persons with 5 of 13 infections studied. In these the incidence of titers above 1 : 56 was higher than for normal controls and in the infections in which the titer did not exceed 1 : 224.

RELATION OF THE COLD AGGLUTININ TITER TO OTHER FEATURES OF PRIMARY ATYPICAL PNEUMONIA

Although it is clearly evident that a high level of serum cold agglutinin is observed in many patients with primary atypical pneumonia, little is known of the significance of this fact and its relation to other features of the syndrome. To obtain some data on these points, we compared the clinical observations with the cold hemagglutinin responses of 44 patients with primary atypical pneumonia. These patients were divided on the basis of cold hemagglutinin titer into three groups: (1) 15 patients with very high titers (1 : 1,792 or above) on admission to the hospital; (2) 13 patients with a rise in titer to a high level after admission, and (3) 16 patients in whom the cold agglutinin titer failed to exceed the highest values for normal controls and for patients with bacterial pneumonia and a variety of infectious diseases (table 2). Following is an analysis of some of the clinical features of each of these groups:

Group 1.—The essential clinical findings for 15 patients with primary atypical pneumonia in whom very high levels of serum cold agglutinin were present on admission are shown in table 6. In most of these cases, the disease was extremely mild and many of the patients seemed to be convalescing from a primary atypical pneumonia unrecognized for several weeks prior to entry. The period between the probable onset of the disease and admission to the hospital varied from five to thirty days (mode, ten to twelve days; average, thirteen days). In each instance, the patient sought admission because of persistent cough or the sudden onset of pain in the chest and fever after a variable period of cough. On admission, 10 patients had little or no fever; 5 patients were afebrile during the entire period of hospitalization, and in the others, the days of fever were usually less than seven. The white blood cell counts on admission varied from 7,300 to 24,600 but were usually between 7,000 and 11,000. The only other frequent hematologic observation was the presence of 4 to 10 monocytes in the differential white cell count (9 of 13 white blood cell counts). Roentgenograms of the chest showed only increased peribronchial and perivascular markings in 3 patients and slight evidences of pneumonic involvement in 9. In 2 of these, the roentgenologic abnormalities cleared in about ten days or less. Ten of these patients were treated symptomatically. Five were given sulfonamide compounds. Although in 1 patient so treated the temperature dropped to normal in twenty-four hours (case 12), in the other 4 the response to sulfadiazine was not dramatic. Eight of these patients left the hospital ten to twenty-one days after entry, with no or minimal residual symptoms or signs. The others were hospitalized longer because of persistent cough or thoracic findings. Pleural effusion was not noted in this group.

The case of 1 of these patients is worthy of special mention because it was very unusual in several respects and illustrates that the cold hemagglutinin response may precede definite roentgenographic evidence of primary atypical pneumonia by several weeks.

CASE 8.—A 20 year old Negro seaman was admitted to the hospital with a history of persistent cough, substernal pain, sore gums and occasional chilly sensations for about two weeks. Two or three days prior to entry, he began to suffer from an intense headache associated with nausea and vomiting.

On admission, he appeared drowsy. His temperature was 99.4 F. (oral), pulse rate 72 and respiratory rate 20. His cervical lymph nodes were palpable bilaterally, but there was no other adenopathy and the spleen could not be felt. The lungs were clear except for a few sticky rales on deep inspiration and after cough at the base of the right lung posteriorly. There was definite nuchal rigidity, and Kernig's sign was positive bilaterally. The only other positive finding was pronounced hypertrophic gingivitis.

Laboratory studies revealed a red blood cell count of 4,750,000, a hemoglobin content of 14.5 Gm., a white

TABLE 6.—*Essential Clinical Observations on Fifteen Patients with Primary Atypical Pneumonia with Very High Cold Hemagglutinin Titers on Admission to the Hospital*

TABLE 6.—*Essential Clinical Observations on Fifteen Patients with Primary Atypical Pneumonia with Very High Cold Hemagglutinin Titers on Admission to the Hospital*

Case No.	History	Admission Temperature, F.	Physical Findings on Examination of Lungs	Roentgenogram of Chest	White Blood Cell Count					Days		Complications and Residuals	Sulfadiazine	Cold Agglutinin Titer on Admission
					Total	Poly.	Lymph.	Eosin.	Mono.	Fever	Hospital			
1	Persistent cough, pain in chest, low grade fever and chilly sensation for 7 days	99	Diminished breath sounds; occasional rales in right lower part of chest posteriorly	Bilateral increase in perivascular and peribronchial markings	8,400	54	36	0	0	2	26	None	0	1:14,000
2	Coryza followed by dry cough for 10 days; sudden onset of pain in chest	98	Dulness; diminished breath sounds at base of left lung posteriorly	.....	7,300	63	33	0	4	0	10	Cough	0	1:7,168
3	Persistent cough; low grade fever for 10 days; sudden onset of pain in chest	99	Diminished breath sounds; coarse rales at base of left lung	Diffuse mottling extreme left base; slight clearing in 11 days	None	..	..	..	..	0	30	Cough, roentgen shadow	0	1:3,584
4	Sudden onset of pain in chest and cough 20 days after onset of previous pneumonia	99	Moist rales at base of left lung	Small area of increased density at base of left lung	None	..	..	..	..	0	20	None	0	1:3,584
5	Coryza followed by cough for 14 days; pain in chest for 3 days	99	Dulness; diminished breath sounds; rales at base of left lung	Small area of increased density at base of left lung lateral to heart border	13,000	84	14	0	1	3	27	None	0	1:3,584
6	Fatigue; generalized aches; malaise; low grade fever 12 days	98.6	Bronchovesicular breath sounds; coarse rales at bases of both lungs	Heavy mottled density lower portion upper lobe right lung and in middle lobe of right lung; increased lung markings on left	7,450	68	26	0	6	2	26	Roentgenogram positive	0	1:3,584
7	Coryza followed by cough for 10 days; sudden onset of pain; in chest; chill; fever	102	Dulness; diminished bronchial breath sounds over entire lower lobe of left lung	Marked increase in density in middle third of left lung; mottled density in upper lobe of right lung	7,500	64	28	2	6	5	27	None	+	1:3,584
8	Slight cough; sore chest; sore gums; fever for 14 days; headache for 3 days	99.4	Diminished breath sounds; rales at base of right lung	Increase in perivascular and peribronchial markings	16,500	74	22	0	4	4	18	None	+	1:3,584
9	Productive cough; malaise for 3 weeks	99	Chest normal	Blunting of left costophrenic angle; increase in peribronchial markings	8,600	48	45	0	7	0	35	None	0	1:3,584
10	Persistent cough; malaise; occasional fever 1 month; sudden onset of pain in chest; chills; fever	98	Diminished breath sounds; rales at base of left lung	Small area (6 cm. in diameter) of increased density at base of left lung	10,950	79	12	4	6	0	21	Cough	0	1:3,584
11	Persistent cough; malaise; sweats; occasional low grade fever for 1 week	100	Diminished breath sounds at base of left lung	Diffuse area of increased density in middle third of left lung; clearing in 10 days	10,700	74	16	0	10	7	21	Cough; pain in chest	0	1:3,584
12	Coryza; cough; low grade fever for 1 week; sudden onset of pain in chest	102	Dulness; diminished breath sounds at base of right lung posteriorly with coarse rales	Irregular area of infiltration in lower lobe of right lung	11,300	89	11	0	0	1	38	Cough	+	1:1,792
13	Headache; cough; chills; arthralgias for 5 days	102	Bronchovesicular breath sounds and rales at bases of both lungs	Mottled area of increased density in middle lobe; cleared in 10 days	13,500	59	32	2	7	5	21	None	0	1:1,792
14	Persistent cough for 16 days; sudden onset of fever	101.6	Bronchial breath sounds; rales at base of left lung	Mottled area of increased density in lower lobe of right lung	24,000	80	18	0	2	6	16	None	+	1:1,792
15	Fever for 2 weeks; cough; pain in chest for 1 week	104	Dulness; rales at base of right lung	Area of increased density at base of right lung medially	10,700	74	16	0	10	3	30	Malnutrition	+	1:1,792

blood cell count of 16,500, with 74 per cent polymorphonuclear leukocytes, 22 per cent lymphocytes and 4 per cent monocytes; examination of the urine for albumin, sugar and formed elements gave negative results, and the erythrocyte sedimentation rate (Cutler) was 24 mm. in one hour. The Kahn reaction of the blood was negative.

A lumbar puncture yielded clear fluid under a pressure of 220 mm., which contained 68 mononuclear cells per cubic millimeter. The Pandy reaction was negative. The spinal fluid contained 48 mg. of protein per hundred cubic centimeters. Culture of the spinal fluid was negative for bacteria.

A roentgenogram of the chest showed an increase in perivascular and peribronchial markings.

Course.—The patient was given sulfathiazole in doses of 1 Gm. every four hours for one week. His temperature became normal in four days, and he became more alert and responsive. A slight cough persisted.

Special Studies.—Examination of the serum revealed a cold hemagglutinin titer of 1:3,584 within twenty-four hours after his admission to the hospital. This rose to 1:7,168 and was still 1:3,584 seventeen days after admission, when the patient returned to duty. A complement fixation test for lymphogranuloma venereum was negative. The patient's serum did not neutralize the viruses of St. Louis and Western equine encephalitis. The heterophile antibody titer was 0. The Weil-Felix reaction with Proteus OX-19 was negative.

Second Admission.—The patient remained free of complaints for a period of five weeks. At the end of this time, he again began to cough, and after one week he suddenly experienced chilly sensations and a sharp pain in his right shoulder on inspiration.

Physical examination now revealed a temperature of 104 F., pulse rate of 92 and respiratory rate of 20. The patient was not dyspneic and did not appear acutely ill. On auscultation of the chest there was a leathery friction rub over the upper lobe of the right lung anteriorly and posteriorly, and the breath sounds were diminished in this area. The percussion note was dull. There were no other positive findings on physical examination.

The white blood cell count was 32,500, with 92 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes and 2 per cent monocytes. Sputum was difficult to obtain and did not reveal pneumococci, tubercle bacilli or other pathogenic bacteria. A spinal puncture revealed a normal spinal fluid pressure and yielded a clear fluid which still contained 14 cells per cubic millimeter. A roentgenogram of the chest now revealed a large homogeneous density involving the upper lobe of the right lung. The patient was given sulfadiazine in doses of 1.5 Gm. every four hours. His temperature fell to normal in five days, but he continued to cough and to complain of pain in the shoulder for an additional five days. The roentgen shadow in the upper lobe of the right lung cleared almost completely in ten days.

The cold hemagglutinin titer on this admission was 1:448 and remained at this level for two weeks, after which the patient returned to duty.

Summary.—In this case an acute meningeal reaction occurred in a patient whose serum revealed a high cold hemagglutinin titer (1:7,168). Although there was some evidence of a pulmonary involvement at this time, on physical examination, an atypical pneumonia was not apparent roentgenographically until about eight weeks later when there was a recurrence of cough and fever associated with pain in the shoulder and a homogeneous density in the right upper lobe.

Group 2.—A rise in cold hemagglutinin titer from low or moderately increased levels to higher ones was observed in 13 patients (table 7). The clinical findings and course varied widely in individual patients, but in general the entire group was characterized by a more acute onset of the syndrome (one to fourteen days) and a febrile course requiring longer periods of hospitalization than in group 1.

A significant increase in cold hemagglutinin titer was often apparent toward the end of the first week after the probable onset of the syndrome. Maximum titers were usually attained during the second and third weeks. However, this was not true of every patient. In 4, a significant increase in titer (above 1:224) was not observed for five or more weeks after the onset, and in 1 patient it did not occur until about in eight weeks (chart 2). In 1 of these cases, a sharp increase in the titer of cold hemagglutinin was associated with a secondary rise in temperature and the occurrence of acute polyarthritis, pro-

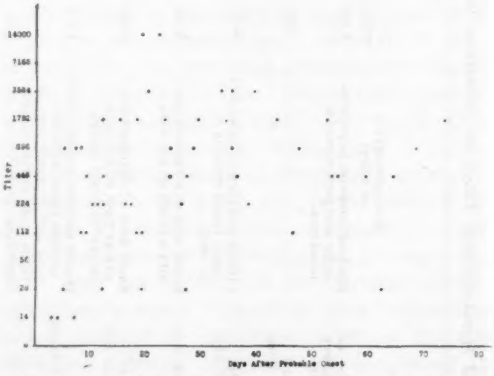

Chart 2.—Relation between time after probable onset and cold hemagglutinin titer of 13 patients with primary atypical pneumonia (table 7).

ducing a syndrome resembling acute rheumatic fever, which has been noted previously in cases of primary atypical pneumonia.[7a] The pronounced rise in the cold hemagglutinin level was maintained only for a short time and fell to lower but still elevated values (1:448) as the fever and polyarthritis subsided. Prior to the recognition in recent years of the syndrome of primary atypical pneumonia, this case might have been considered as an example of rheumatic pneumonia.

A comparison of the findings and course of the 7 patients in whom the titer rose to high levels within three weeks and of the 6 in whom the rise in titer required a longer period indicated that the former had a shorter febrile course, with fewer complications and residuals.

Although based on observations on only a few patients, it is our general impression that a very

TABLE 7.—*Essential Clinical Observations on Patients with Primary Atypical Pneumonia Showing Rising Cold Hemagglutinin Titers*

TABLE 7.—*Essential Clinical Observations on Patients with Primary Atypical Pneumonia Showing Rising Cold Hemagglutinin Titers*

Case No.	History	Admission Temperature, F.	Physical Findings on Examination of Lungs	Roentgenogram of Chest	White Blood Cell Count					Days		Sulfadiazine	Complications and Residuals	Cold Agglutinin Titer on Admission	Days After Onset	Highest Cold Agglutinin Titer	Days After Onset
					Total	Poly.	Lymph.	Eosin.	Mono.	Fever	Hospital						
1	Dry cough, low grade fever for 1 week	101.6	Moist musical rales, over entire left lung	Area of ill defined density at base of right lung; cleared in 9 days	18,800	88	8	2	2	1	27	0	None	1:448	12	1:1,792	18
2	Low grade fever for 4 days; cough for 1 day	101	Lungs clear	Small area of increased density at base of left lung just above diaphragm	4,100	72	24	0	4	4	12	0	None	1:14	4	1:448	9
3	Dry cough, fever; pain in chest for 2 days	100.6	Diminished breath sounds; fine rales at base of right lung; to and fro rub	Small infiltration in lower lobe of left lung	10,450	86	14	0	0	3	14	0	None	1:896	5	1:1,792	12
4.	Dry cough, low grade fever for 1 week	101	Coarse wheezes; rales over both pulmonary fields	Early infiltration just above diaphragm on left	11,700	70	30	0	0	4	57	0	Mumps 1 month after admission	1:896	7	1:3,584	20
5	Dry cough for 1 week after recovery from measles	98.6	Coarse rales at bases of both lungs	Ill defined infiltrations in base of left lung extending to left hilus	12,200	64	26	0	0	14	26	0	Acute sinusitis; persistent cough	1:896	8	1:14,000	19
6	Sudden onset of dry cough, fever, chill, pain in right side of chest	102	Coarse rales, to and fro rub at base of right lung	Homogeneous density of upper lobe of right lung; cleared in 17 days	17,450	83	16	1	0	5	22	+	None	1:14	3	1:1,792	22
7	Slight cough, low grade fever, headache for 4 days	102	Chest clear	Fine mottling at base of left lung; cleared in 2 days	8,800	69	29	0	2	6	18	0	Slight	1:224	10	1:14,000	22
8	Cough, fever, chill, sore throat for 4 days	104	Dulness, bronchial breath sounds, friction rub at base of right lung	Area of increased density at base of right lung laterally	26,600	62	36	0	2	7	16	+	Pleurisy	1:14	7	1:448	24
9	Cough, fever, malaise, arthralgias for 2 days	101	Small area of bronchial breathing at base of right lung	Area of increased density at base of right lung medially	9,400	54	52	0	4	11	60	0	Acute arthritis; persistent cough	1:112	8	1:448	27
10	Sudden onset of fever, chill, pain in chest after cough and measles 2 weeks before	104	Bronchial breath sounds, dulness, to and fro friction rub at base of right lung	Area of increased density at base of right lung, extending from diaphragm to second rib	42,500	96	2	0	2	19	36	+	Pleural effusion	1:112	18	1:3,584	35
11	Malaise, low grade fever for 1 week; sudden onset cough, pain in right side of chest	105	Dulness, diminished breath sounds, rhonchi at base of right lung	Area of increased density in upper part of lower lobe of right lung	17,300	91	6	0	3	30	53	+	Pleural effusion; persistent cough; arthritis	1:112	9	1:3,584 1:448	40 55
12	Dry hacking cough for 4 weeks following acute catarrhal fever; sudden onset of pain in chest, high fever, sputum	100.6	Dulness, diminished breath sounds below angle of left scapula	Small area of increased density extreme left base; cleared in 1 week	6,800	56	36	2	2	1	19	0	Cough	1:448	36	1:1,792	42
13	Headache, low grade fever, pain in chest for 3 days	102	Dulness, diminished breath sounds at base of left lung	Small area of increased density at base of left lung	17,000	80	18	0	2	63	73	+	Pleurisy; persistent cough	1:28	5	1:1,792	73

high cold hemagglutinin titer on admission to the hospital or a rapidly rising titer (within two or three weeks) seemed to herald a favorable prognosis. On the other hand, a slowly rising titer of cold hemagglutinin was usually indicative of a prolonged illness.

Group 3.—In 16 patients, followed for periods of twenty-two to sixty-one days after the probable onset of the syndrome, the cold hemagglutinin titer did not rise above the highest values seen in normal controls and in patients with a variety of acute infections (1:112 or 1:224). Although cold hemagglutinin was demonstrated in each of these patients, in 7 the titer failed to exceed 1:56 and in 9 it rose slowly to 1:112 and 1:224 or remained fixed at these levels (table 8).

In this group, the clinical findings were similar to those of the sicker patients in group 2 (with a slowly rising titer). Three patients gave a history of a previous attack of pleuritic pain and fever within the past year. One patient was seen with a recurrence of fever, pain in the chest and cough immediately after a thirty day period of hospitalization for primary atypical pneumonia.

Ten patients were admitted within seven days after the onset of symptoms; 6 patients had symptoms for a longer period prior to entry. All were febrile on admission, and in ten the admission temperature was 102 F. or above. The white blood cell counts varied from 4,150 to 14,100 and were below 9,000 in 10 patients. Only 1 patient had more than 4 monocytes in the differential count. The roentgenologic observations did not differ from those of some of the patients in the other groups with primary atypical pneumonia, and the response to sulfadiazine was disappointing.

The febrile course was usually prolonged and exceeded one week in 9 cases. Seven patients had low grade fevers (temperatures up to 101-102 F.) for two to six weeks. The periods of hospitalization were correspondingly long and were more than twenty-one days for 11 patients. Eight of these patients still complained of cough when they left this hospital. Four had pleural effusions requiring further convalescent care.

Although the syndrome seemed somewhat more prolonged in this group and the incidence of complications and residual symptoms was higher, the only striking difference was the failure of the cold hemagglutinin level to reach the increased values observed in 60 per cent of the patients with primary atypical pneumonia. The reasons for this were not apparent, but the following possible explanations were considered: 1. Certain etiologic agents causing the syndrome of atypical pneumonia may fail to call forth a cold hemagglutinin response. 2. In certain patients with primary atypical pneumonia, the response may not occur for long periods (as in case 10, group 2). 3. In some instances it may have been impossible to distinguish between primary atypical and bacterial pneumonia.

COMMENT

This study confirms previous observations that human serum frequently contains a cold hemagglutinin for homologous erythrocytes (group O).[9] As suggested by Kettel,[10] this may be a universal property of human serum. With a method involving a long period of refrigeration of the cell suspensions and a microscopic reading of the end point, cold hemagglutination was commonly noted in normal serum dilutions through 1:56. Slightly higher values (1:112 and 1:224) were observed occasionally in the serums of normal persons (11 per cent). It seemed logical to regard these higher values as possible reactions to recent acute infectious diseases, since it is known that the serum cold hemagglutinin level increases during convalescence from certain infections, for example, primary atypical pneumonia.

If it is assumed that a titer of 1:56 is the upper limit of cold agglutinin activity in most normal serums with this serologic method, then slight increases in titer were noted in the serums of patients with almost every infection studied. This suggests a nonspecific stimulation of the tissues involved in the production of cold hemagglutinin by a wide variety of infectious agents. On the other hand, since great increases in cold hemagglutinin titer were observed in the serums of patients with a smaller group of diseases, it seemed that certain infectious agents are capable of eliciting a more intense reaction of this type than others. However, these intense responses as well as the mild ones were relatively nonspecific.

Although the mechanism of the production of cold hemagglutinin in large amounts in persons with certain infectious diseases is unknown, many of the conditions in which this was noted are characterized by the appearance of large amounts of specific antibodies in the serum. In these conditions cold hemagglutination may be a manifestation of the presence of distinct but chemically related antibodies. Another explanation, suggested by Belk,[11] who studied a cold agglutinin in a case of infectious mononucleosis,

9. Kettel, K.: Recherches sur les agglutinines au froid dans les serums humains, Compt. rend, Soc. de biol. **100**:371, 1929.

10. Kettel, K., cited by Stats and Wassermann.[5]

11. Belk, W.: Minor Hemagglutinins, J. Lab. & Clin. Med. **20**:1035, 1935.

TABLE 8.—*Essential Clinical Observations on Sixteen Patients with Primary Atypical Pneumonia with Low*

TABLE 8.—*Essential Clinical Observations on Sixteen Patients with Primary Atypical Pneumonia with Low Cold Hemagglutinin Titers*

Case No.	History	Admission Temperature, F.	Physical Findings on Examination of Lungs	Roentgenogram of Chest	White Blood Cell Count					Days		Sulfadiazine	Complications and Residuals	Highest Cold Agglutinin Titer	Days After Probable Onset
					Total	Poly.	Lymph.	Eosin.	Mono.	Fever	Hospital				
1	Chronic cough with yellow, blood-streaked sputum for 2 weeks; chills, fever, pain in chest for 1 day	102	Dulness, diminished breath sound at base of left lung; rales at bases of both lungs	Small area of consolidation at base of right lung medially	8,700	61	37	0	2	5	30	+	Slight cough	1:28	44
2	Sudden onset of cough, fever, chills 2 days before admission	100	Dulness, diminished breath sounds at base of left lung and upper lobe of right lung	Area of increased density in upper third of right pulmonary field	5,600	58	40	0	2	2	27	0	Slight cough	1:56	44
3	Productive cough, pain in left side of chest for 2 weeks; acute pain in chest on inspiration for 2 days	101.8	Dulness, diminished breath sounds at base of left lung	Small area of increased density at base of left lung laterally; fluid present 1 week after admission	7,100	69	27	2	2	27	34	0	Pleural effusion	1:112	48
4	Dry cough, malaise, anorexia, low grade fever for 10 days; pain in chest for 8 days; pleurisy 1 year ago	100	Fine crepitant rales at base of right lung; rhonchi throughout both lungs	Area of increased density in middle third of left lung	8,700	72	26	2	0	5	26	+	None	1:112	35
5	Persistent productive cough for 2 weeks, bloody sputum 2 days before admission	103.6	Roughened breath sounds, bubbling rales at base of left lung	Small area of increased density overlying domes of diaphragm on each side; clear in eleven days	7,300	50	40	2	8	7	21	+	None	1:112	35
6	Pain in right side of chest and dyspnea after acute catarrhal fever for 1 week	99.5	Dulness, bronchial breathing, fine rales at base of right lung	Obliteration of right costophrenic angle and diffuse infiltration in this area	10,500	68	28	0	4	14	72	+	Persistent cough and weakness	1:224	61
7	Cough, chilly sensations, low grade fever for 2 weeks; sudden onset of high fever	104.5	Scattered rhonchi bilaterally; fine rales at angle of left scapula	Area of increased density left midpulmonary field; blunting of right costophrenic angle	7,900	70	28	0	2	11	17	+	None	1:56	31
8	Productive cough for 1 week; chills, fever for 1 day	103	Sonorous rales at bases of both lungs	Small area of increased density at base of left lung; no evidence of bronchiectasis	11,150	64	34	0	2	36	36	0	Serofibrinous pleurisy, cough, rales on discharge	1:28	40
9	Sudden onset of cough, fever, chest pain on inspiration; similar attack 2 months previously	103.2	Dulness, diminished breath sounds at base of right lung and in right scapular region	Area of increased density in upper lobe of right lung	12,600	80	18	0	2	14	26	+	Pleuritic pain, late in convalescence, with fever	1:28	23
10	Persistent cough for 1 week; sticking pain in left side of chest for 1 day	101	Diminished breath sounds, fine rales at bases of both lungs	Area of increased density at base of right lung medially; no change in 1 week	8,600	67	31	0	2	16	30	0	Persistent cough	1:112	27
11	Dry cough, pain in right side of chest for 1 week	99	Dulness, decreased breath sounds at base of right lung	Area of increased density at base of right lung; some obliteration of left costrophrenic angle	11,500	80	20	0	0	9	20	+	None	1:28	22
12	Severe productive cough, malaise, low grade fever for 2½ weeks; pain in chest for 1 day	100	Rales at bases of both lungs	Multiple areas of increased density at bases of both lungs	12,000	73	25	0	2	18	26	0	Productive cough	1:56	26
13	Recurrence of pain in left side of chest, chills, fever for 1 day, 1 week after attack of atypical pneumonia	99	Dulness, diminished breath sounds in lower lobe of left lung	Area of increased density in middle lobe and at base of left lung; some fluid 1 week later	6,800	44	50	2	4	6	30	+	Cough	1:112	49
14	Sudden onset of fever, chills nonproductive cough 20 hours previously	103	Few coarse rales at base of left lung	Exaggeration bronchial markings in both lungs; massive pleural effusion	10,500	86	12	0	2	40	46	+	Massive pleural effusion	1:224	30
15	Coryza, low grade fever for 6 days, followed by sudden onset of fever, chill, pain in right side of chest	104	Dulness, bronchovascular breath sounds, occasional rhonchi at base of left lung	Increased density in mid portion of left pulmonary field	4,150	70	38	0	2	6	28	+	None	1:224	25
16	Chronic cough for 1 month; sudden onset of high fever, productive cough, pain in chest	103.4	Mild dyspnea; dulness, bronchial breath sounds at base of left lung	Increased density in lower third of left pulmonary field	13,100	88	8	0	4	7	21	+	Hemorrhagic sterile pleural effusion	1:112	54

is that cold hemagglutination is due to purposeless and excessive production of antibodies under certain conditions of nonspecific stimulation.

A further point in favor of the nonspecific, or general, character of the phenomenon of cold hemagglutination in infectious diseases is the fact that the serums in which it occurs to a significant degree frequently react positively for syphilis. These reactions are common in trypanosomiasis, malaria and infectious mononucleosis and have been observed in other acute infections, including primary atypical pneumonia.[12] Moreover, a reagin of the type giving a positive Kahn or Wassermann reaction has been found in small amounts in normal human serums and at times in sufficient quantity to give a positive reaction for syphilis in a perfectly normal person.[13] It is interesting and perhaps has some bearing on the nature of cold hemagglutination that the general biologic type of Kahn precipitation reaction occurs strongly at 1 C. while the true syphilitic reagin is maximally active at 37 C. and inactive at 1 C.[14] The apparent relation of nonspecific serologic reactions to low temperatures is further indicated by the finding that cold seems to increase the activity of sheep cell agglutinins in infectious mononucleosis.[14]

The frequent presence of extremely high titers of cold hemagglutinin in persons with primary atypical pneumonia alone of the common diseases of the respiratory tract studied is a serologic observation of value in confirming the diagnosis of the syndrome in most cases and in differentiating it from pneumonia of other common causes. However, the characteristic sharp elevations in cold agglutinin concentration were not observed in an appreciable number of persons with primary atypical pneumonia. In our opinion, the test was of least value as a differential finding in cases in which the greatest difficulty was encountered in distinguishing primary atypical from bacterial pneumonia. It is possible, however, that some cases in which slight elevations in titer were noted in convalescence were instances of infections with more than one agent (i. e. virus and bacteria).

A correlation of the cold agglutinin response and the clinical observations in cases of primary atypical pneumonia indicated that this reaction may have prognostic value. The type of response seemed to be related to the course of the disease. It occurred promptly and was most intense in the cases of mild disease and slow in developing and often slight in the cases in which the course was prolonged and marked by complications. This behavior of the cold hemagglutinin response favors the concept that it is a manifestation of immunity.

The test in our hands has been of definite assistance in case finding and has led to the recognition of several cases of mild primary atypical pneumonia that may not have been noted if this test had not been done. Titration of the serum for cold hemagglutinin is advised for all patients with persistent cough and obscure pulmonary abnormalities on physical and roentgenographic examination. The failure to observe high titers of cold agglutinin in patients with a variety of minor infections of the respiratory tract and in a group of normal persons who had recently recovered from such infections suggests that it is of doubtful value in detecting the carrier state and minor infections with the agent or agents causing atypical pneumonia. However, since we had no data concerning the number of actual infections with or exposures to such agents, an evaluation of the test as a tool in studying the epidemiology of primary atypical pneumonia must await the definite recognition of the agents causing the syndrome.

SUMMARY

1. A cold hemagglutinin against human group O erythrocytes was detected in 72 per cent of 472 subjects, including 115 with pneumonia, 257 with other infections and 100 normal controls.

2. In normal controls, the cold hemagglutinin titer was usually 1:56 or lower (89 per cent) and reached 1:112 and 1:224 in 11 per cent. Recovery from recent acute infection seemed significantly to affect the cold hemagglutinin level of the serum in normal controls.

3. The highest values of cold hemagglutinin were found most frequently in patients with primary atypical pneumonia, but in 40 per cent of persons with this syndrome the titer did not exceed the highest titer (1:224) in normal controls and in persons with a variety of acute infections.

4. In patients with bacterial pneumonia, the cold hemagglutinin values were usually lower than in patients with primary atypical pneumonia. Slight elevations in titer equaling the highest titer in 25 per cent of the patients with atypical pneumonia occurred in patients with bacterial

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13. Kahn, R. L.: The Verification Test in the Serology of Syphilis, J. Lab. & Clin. Med. **28**: 1175, 1943.

14. Spingarn, C.; Jones, J. P., and Owrutsky, B.: A Note on the Occurrence of Cold Hemagglutination in Infectious Mononucleosis. U. S. Nav. M. Bull. **43**: 717 (Oct.) 1944.

pneumonias complicated by empyema or pleural effusion.

5. High values of cold hemagglutinin were noted in patients with infectious mononucleosis, mumps orchitis, measles, scarlet fever and rheumatic fever.

6. In patients with primary atypical pneumonia, a high titer on admission or a rapidly rising titer seemed to indicate a favorable prognosis.

7. Patients with primary atypical pneumonia in whom high titers of cold hemagglutinin were not observed usually had a prolonged illness in which pleural complications were frequent.

8. It is possible that cold hemagglutination is a nonspecific manifestation of certain types of antibody response.

Captain J. H. Robbins, MC, U.S.N., the Commanding Officer of the Naval Hospital, Treasure Island, and Captain E. J. Best, MC, U.S.N.R., Chief of Services, gave advice in this study. Dr. G. Meiklejohn performed the complement fixation and neutralization tests in case 8. Valuable technical assistance was given by Chief Pharmacist Mates B. Owrutsky, J. Coyner, L. Dodge and Pharmacist Mates, First Class, S. Spangler and H. Spikes.

AMEBIC PERICARDITIS

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Pericarditis is a rare complication of amebiasis. A review of the literature revealed only 22 proved cases.[1] The literature contains a number of reports of pericardial involvement in the course of hepatic abscess of probable, but not proved, amebic nature. Some of these cases occurred before the discovery of Endameba histolytica.

In a recent review amebic hepatitis and hepatic abscess were extensively discussed by Ochsner and DeBakey.[1a] These authors stated that various surveys of the population of the United States have shown the incidence of amebiasis to be between 5 and 20 per cent. The incidence of associated hepatitis and hepatic abscess varies considerably in different statistical analyses. As was pointed out by Ochsner and DeBakey, this incidence is significantly higher in the cases in which autopsies were performed than in the clinically observed cases. These authors collected a series of 5,211 fatal cases of amebiasis and noted that in 36.6 per cent of these the liver was involved. The incidence in the various groups of this series varied between 7.6 and 84.4 per cent. In a series of 9,696 cases of clinical amebiasis assembled from the literature, hepatic abscess was present in 4.86 per cent.

The purpose of this report is to present a case of amebic pericarditis secondary to extension of an amebic abscess of the liver. In this case the correct diagnosis was made only at autopsy.

From the Departments of Pathology of Grady Hospital and Emory University School of Medicine.

1. (*a*) Ochsner, A., and DeBakey, M.: Amebic Hepatitis and Hepatic Abscess, Surgery **13**: 460 (March); 612 (April) 1943. (*b*) Vergoz and Hermenjat-Gerin: De la rupture des abcès amibiens du foie dans les cavités séreuses (plèure, péritoine, péricarde), Rev. de chir., Paris **51**: 680 (Nov.) 1932. (*c*) Huard, P., and Meyer-May, J.: Les abcès du foie, Paris, Masson & Cie, 1936. (*d*) Craig, C. F.: The Complications of Amoebic and Specific Dysentery, as Observed at Autopsy: An Analysis of One Hundred and Twenty Cases, Am. J. M. Sc. **123**:145 (Aug.) 1904. (*e*) Howard, W. T., and Hoover, C. F.: Tropical Abscess of the Liver, ibid. **114**:150 (Aug.) 1897. (*f*) Surbek, K. E.: Ein Fall von Amöben-Pericarditis, Arch. f. Schiffs- u. Tropen-Hyg. **34**:456 (Aug.) 1930. (*g*) Kataropula, A.: Amöbenperikarditis, ibid. **36**: 544 (Oct.) 1932.

REPORT OF A CASE

History.—A 17 year old Negro entered Grady Hospital in March 1944. Because of pain and tenderness in his left flank and costovertebral angle, he was admitted to the genitourinary service with a diagnosis of perinephric abscess.

The patient had been in apparently good health until three months prior to admission to the hospital; at that time he noted the gradual onset of pain in the right shoulder, which persisted intermittently until his admission. During the same period he complained of malaise and progressive loss of appetite and of weight. Approximately two months prior to admission he noticed pain in the lumbar region, at first in the midline. It rapidly spread to both flanks and was particularly severe on the left. During the three weeks preceding admission he had profuse nocturnal sweats and fever without chills. He occasionally noted a pain in both sides of the chest but had no cough. In the week before admission he frequently complained of periumbilical pain and of a sharp pain in the left flank, which radiated toward the left axilla.

There was no history of diarrhea, and the remainder of the review of the systems failed to reveal anything significant.

The past history and the family history were noncontributory.

Physical Examination.—On his admission the patient's temperature was 100.8 F., his pulse rate 105 per minute, his respiratory rate 22 per minute and his blood pressure 90 systolic and 60 diastolic. He was acutely ill. The significant physical findings were limited to the chest and the abdomen.

The heart was slightly enlarged to the left, and there were a loud pleuropericardial friction rub and a thrill over the lower left side of the precordium. No murmurs were heard. There was normal sinus rhythm. A few moist rales were heard over the bases of both lungs, especially the right; otherwise the lungs showed no abnormalities on physical examination. There was tenderness in both flanks and costovertebral angles, more marked on the left. The liver was palpated 4 finger-breadths below the right costal margin; it was not tender.

Laboratory Data.—On the patient's admission the only significant laboratory finding was a white blood cell count of 20,800, with 86 per cent neutrophils and 14 per cent lymphocytes. The count ranged from 13,000 to 39,000 on many subsequent examinations during his thirty-nine day stay in the hospital. The results of urinalysis were essentially normal at all times. There was mild secondary anemia. The erythrocyte sedimentation rate was 64 mm. in one hour (Westergren). The Kahn reaction of the blood was negative. Examination of the stool failed to show the presence of blood (guaiac test). Repeated cultures of blood were sterile. A tuberculin test (purified protein derivative, first strength) elicited a positive reaction. A retrograde pyelogram and a roentgenogram of his chest

taken the day after his admission were interpreted as normal. A lumbar puncture yielded no significant information.

Course.—During the first six days in the hospital the patient's temperature varied between 100 and 102 F.; clinically there was no significant change except for development of a sharp precordial pain on the sixth day. On the next day this became severe, and there were signs of peripheral circulatory collapse, with a blood pressure of 70 systolic and 60 diastolic. The veins of his neck were distended, and his pulse was strikingly paradoxic. A roentgenogram of his chest at this time revealed that the heart was considerably larger than previously, with a shortened cardiac pedicle. On fluoroscopic examination no pulsations of the ventricles could be seen. Pleural thickening along both axillary lines and a small area of increased density in the right costophrenic angle were also reported.

A diagnosis of pericardial effusion was made, and the patient was transferred to the medical service, where an immediate pericardial paracentesis resulted in dramatic clinical improvement. Six hundred cubic centimeters of thin, chocolate-colored material was withdrawn. This fluid contained 45,000 red blood cells and 110,000 white blood cells, 88 per cent of which were polymorphonuclear leukocytes. Frequent pericardial taps were performed thereafter; several of them were necessitated by symptoms of tamponade. Each time 250 to 850 cc. of fluid was removed; this became progressively thicker and changed from chocolate brown to brick red. The number of white blood cells in this exudate fell to 8,000 per cubic millimeter, with 44 per cent polymorphonuclear leukocytes. The fluid was cultured repeatedly on routine mediums, as well as on Petragnani's medium, and was sterile at all times. Numerous smears were examined for tubercle bacilli and other bacteria, but none were seen. Several wet preparations of this material were studied by competent observers, and no parasites were noted. On the patient's ninth day in the hospital the entire right pleural cavity was found to be filled with fluid. Despite a thoracentesis, this reaccumulated rapidly. This fluid was clear and straw colored, and a culture of it was sterile. The patient had gross hemoptysis on the twenty-seventh day in the hospital, but this condition lasted for only a few days and the amount of sputum was small. His temperature fluctuated between 98 and 102 F. He was treated with sulfamerazine for one week, without improvement; thereafter, therapy was symptomatic.

Repeated roentgenographic examinations of his chest revealed that his heart had become globular and had remained large. Several electrocardiograms taken after the development of pericarditis showed only isoelectric T waves in leads I and II.

His liver decreased slightly in size, and a small amount of fluid appeared in the peritoneal cavity shortly before death. The pleuropericardial friction rub persisted. The course was downhill, and the patient died on the thirty-ninth day in the hospital. Despite failure to identify the tubercle bacillus by culture or smear, the clinical impression at the time of death was tuberculous pericarditis.

Autopsy.—Autopsy was performed six hours after death. Permission for examination of the brain was not granted. Only the pertinent data are given here.

Gross Examination: The parietal pericardium was thickened and measured 4 to 5 mm. in thickness. The pericardial cavity contained a few cubic centimeters of thick, greenish-yellow, odorless purulent material, which was adherent to both the visceral and the parietal surface. These were yellowish gray and granular. The epicardium was also greatly thickened, and the usual landmarks were obscured. There were no pericardial adhesions. Extensive fibrinous pleuropericardial adhesions were seen on both sides. The right pleural cavity contained 3,700 cc. of light chocolate brown fluid, and the pleural surfaces were covered by shaggy, friable, greenish yellow exudate. The right lung (370 Gm.) was collapsed and displaced toward the mediastinum. The interlobar septums were obliterated by dense fibrinous adhesions. The lower lobe was consolidated, and its posterior lateral third consisted of friable, somewhat necrotic, greenish gray to greenish brown tissue, in which there were numerous rather poorly demarcated abscesses. These varied in diameter from 0.5 to 2 cm. and were filled with viscous, greenish yellow material. In addition, there were several firm, elevated, brownish red nodules. The upper and middle lobes were atelectatic. The left lung (200 Gm.) and the pleural cavity appeared normal.

The peritoneal cavity contained 200 cc. of clear yellow fluid. The liver weighed 1,200 Gm. In the right lobe of the liver, immediately beneath the diaphragm, there was a large abscess. This measured 11 cm. in width, 5 cm. in anteroposterior diameter and 5 cm. in depth. The diaphragm could not be definitely identified in this region. The pericardium appeared to form the superior wall of the abscess, and it extended laterally beneath the right diaphragmatic pleura. The abscess was filled with friable, yellowish green material, similar to that in the pericardial cavity. The inferior vena cava passed through the center of the abscess, and shaggy exudate was adherent to it. A firm, grayish white wall, 3 to 4 mm. thick, separated the abscess cavity from the surrounding hepatic parenchyma, which was compressed, greatly congested and scarred. The remainder of the liver was congested, and its lobular pattern was not distinct. Numerous tiny nodules were palpated on its cut surfaces, but these could not be seen. No communication could be demonstrated between the hepatic abscess, on the one hand, and the pericardial or the pleural cavity, on the other. There was no bronchopleural, bronchohepatic or bronchopericardial fistula.

Careful examination of the entire alimentary tract, from the esophagus to the anus, failed to reveal any evidence of ulceration, inflammation or scarring. There were no other significant findings on gross examination of the heart, spleen, pancreas, kidneys, adrenals, aorta, gallbladder, bladder, genitalia and other structures.

Escherichia coli was cultured from the pericardial cavity, the right pleural cavity, the right lung and the spleen.

Histologic Examination: Blocks of all tissues were fixed in Zenker's fluid with 5 per cent glacial acetic acid and in solution of formaldehye U. S. P., diluted 1 to 10. The phloxine-methylene blue stain was used routinely, and phosphotungstic acid hematoxylin (Mallory's modification for amebas) was used when indicated.

Both the parietal and the visceral pericardium were considerably thickened. They consisted in general of rather dense fibrous connective tissue, but in some areas this was loosely arranged. The surfaces were covered by a thick layer of necrotic material backed by granulation tissue, with numerous large mononuclear cells and some lymphoid and plasma cell elements and a few polymorphonuclear leukocytes. Within the necrotic material the ghostlike outlines of the involved tissues could still be made out. The granulation tissue immediately adjacent to the necrotic material showed evidence of similar lytic necrosis (fig. 1 *A*). Innumerable typical amebas were noted in the necrotic tissue and in the deeper layers of the pericardium but none in the other

layers of the heart. They were also common in the capillaries and small veins. The amebas were found singly and in clusters of three or four (fig. 1 *B*). They were always surrounded by a small halo of cytolysis. They frequently contained phagocytosed red blood cells.

pericardium, which showed varying degrees of obliterative changes. There were no other significant findings in the heart.

The pleura was thickened and fibrosed. Its surface was covered by necrotic material, similar to that described in the pericardium. It also contained numer-

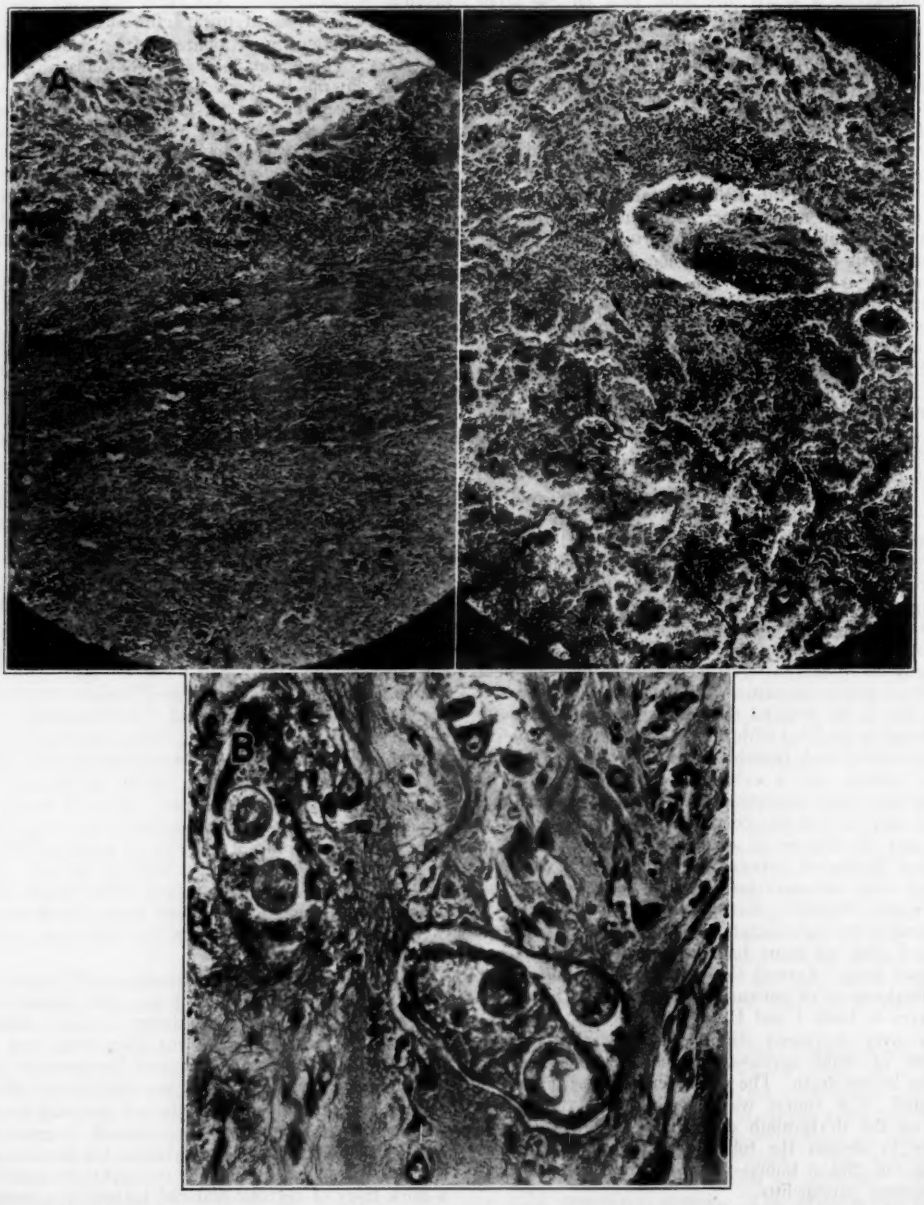

Fig.1.—*A*, parietal pericardium covered on the cardiac surface with a thick layer of exudate. Note the characteristic lytic necrosis of the tissue and the comparatively slight degree of inflammatory cell infiltration. Phloxine–methylene blue; × 60. *B*, several amebas within a capillary of the parietal pericardium. Phosphotungstic acid hematoxylin; × 520. *C*, early amebic abscess in the right lung, involving a bronchus. Relatively uninvolved pulmonary tissue is seen in the upper part of the picture. Phloxine-methylene blue; × 60.

The myocardium immediately beneath the epicardium was pale and edematous. The blood vessels were normal with the exception of some in the deeper layers of the

out typical amebas, and there was evidence of beginning organization. Throughout the pulmonary parenchyma there were numerous abscesses of varying size and age

(fig. 1 *C*). Many of the abscesses appeared to be confluent, and the bronchi were often involved. Early abscesses were characterized by lytic necrosis of the tissue, some hemorrhage and fibrosis, but there was little cellular response. The older abscesses showed ragged walls of fibrous tissue lined with necrotic material, as previously described. Numerous amebas were seen in the abscesses and their walls (fig. 2 *A*). The involved bronchi showed chronic inflammation of their walls and contained many amebas in the lumens and walls. The intervening, uninvolved, parenchyma displayed edema, congestion and numerous large, pigment-laden mononuclear cells in the alveoli, as well as chronic bronchitis. There were no other significant findings in the lungs.

The abscess in the liver was located close to the capsule, which it involved. The abscess wall and its contents displayed the same characteristics as were described in the lung and the pericardium (fig. 2*B*); and, again, amebas were numerous in the wall, as well as among the necrotic contents. The hepatic tissue surrounding the abscess showed marked distortion of its architecture, with extensive old and recent hemorrhages. Elsewhere the architecture of the liver was greatly altered; this change was caused by extensive old scarring of irregular distribution. In some areas it appeared to involve the centrolobular and midzonal areas more than the portal spaces. No significant amount of proliferation of bile ducts had taken place, but in many regions the hepatic cells had a definitely regenerative appearance. No amebas were seen outside the abscess. There were pronounced congestion and edema throughout, with increased activity of the Kupffer cells.

Other histologic changes noted included slight diffuse fibrosis of the spleen, hyperplasia of the bone marrow and slight chronic cystitis. Sections of the stomach and the large intestine were normal. The wall of the gallbladder was slightly edematous, but there was no evidence of an inflammatory process. The tracheobronchial and mesenteric lymph nodes showed hyperplasia but no amebiasis.

Anatomic Diagnosis: The diagnosis was amebic abscess of the liver; amebic pericarditis; amebic pleuritis on the right side; multiple amebic abscesses of the right lung; fibrosis of the liver (weight, 1,200 Gm.); fibrosis of the spleen (60 Gm.); bilateral fibrinous pleuropericardial adhesions; ascites (200 cc.); pronounced congestion of the viscera; hyperplasia of the bone marrow, and emaciation.

COMMENT

The patient's clinical picture was dominated by the obvious pericarditis. Because of this, little attention was paid to the history of pain in the right shoulder three months prior to his admission and the abdominal pain shortly preceding his entry, two symptoms which should have directed attention toward a possible hepatic abscess. Similarly, the important roentgenologic finding of a bilaterally elevated diaphragm was not given proper consideration. All of these findings might have called attention to a hepatic or subdiaphragmatic abscess. In addition, the appearance of the material aspirated from the pericardial cavity should, at least in retrospect, have cast doubt on the diagnosis of tuberculous pericarditis. This material was thin and chocolate colored and corresponded to the characteristic description of the contents of an amebic abscess of the liver.

Although this fluid was examined by observers well acquainted with the appearance of amebas, none were found. However, the diagnosis of amebiasis was not entertained at this time. It is sometimes stated that amebas are not encountered in the contents of a hepatic abscess

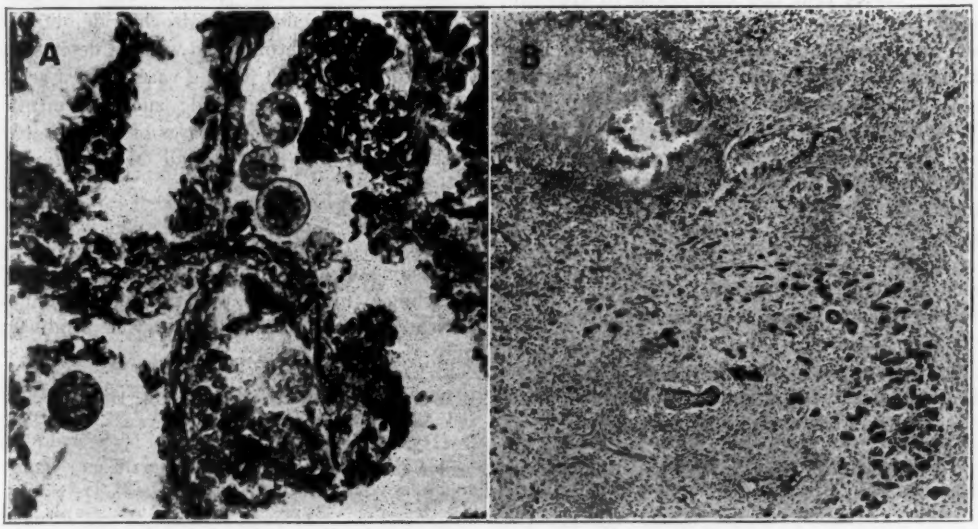

Fig. 2.—*A*, several amebas within the alveoli. The septums show early lytic necrosis. Phosphotungstic acid hematoxylin; × 412. *B*, a corner of the amebic abscess of the liver surrounded by a thick layer of old granulation tissue. Some bile ducts and hepatic cells are seen in the lower right corner. Phloxine-methylene blue; × 50.

but appear only in its wall. MacCallum [2] pointed out that this may be true at the time of the first aspiration but after the abscess has been exposed to air amebas rapidly appear in its contents. In this case, as has already been described, histologic examination revealed numerous amebas in the necrotic material, as well as in the wall of the abscess. Of 873 cases of amebic abscess of the liver collected from the literature by Ochsner and DeBakey,[1a] amebas were demonstrated in the contents of the abscess in 37.8 per cent. However, in their own series of 91 cases in which such an examination was performed positive results were obtained in only 16.5 per cent.

Rupture of an amebic abscess of the liver into the lung, the pleural cavity or both is not an uncommon complication. Ochsner and DeBakey [1a] stated that this may occur in approximately 15 per cent of cases. In the present case, an extension of the amebic infection from the liver into the pericardium, the right pleural cavity and the lung had occurred. Furthermore, the pulmonary amebic abscesses showed extensive communication with the bronchi, many of which contained numerous amebas. Thus there existed the possibility of a more generalized amebic pneumonia involving both lungs and of a secondary involvement of the alimentary tract by swallowing the organism. However, there was no evidence of such a spread of the infection.

It is of interest that no signs of active or healed intestinal amebiasis were encountered in this case. It should be kept in mind that healed lesions in the intestine may be overlooked.

The gross and histologic appearance of the liver in this case was somewhat unusual. It was characterized by fibrosis which did not conform to any of the usual types of cirrhosis of the liver or to that of chronic passive congestion. On the whole the picture suggested the end stage of marked diffuse hepatitis, and one might assume that this had been amebic in nature. Ochsner and DeBakey,[1a] in discussing the histopathology of amebic hepatitis, mentioned a similar observation.

Huard and Meyer-May [1c] reported recovery of a patient with proved amebic pericarditis secondary to a hepatic abscess. Their patient was treated with open drainage of the pericardium. Purcell,[3] as well as Laigret,[4] reported a case of amebic abscess of the liver with signs of pericardial effusion. Their patients recovered under treatment with emetine hydrochloride, but the nature of the pericardial fluid was not determined. It is probable that in these 2 cases only a serous pericardial effusion existed; such an effusion was noted in 6 of the 150 cases of abscess of the liver reported by Huard and Meyer-May.

SUMMARY

In a case of amebic pericarditis subsequent to extension of an amebic abscess of the liver, the clinical impression was that of tuberculous pericarditis, and the diagnosis was established only at autopsy.

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3. Purcell, F. M.: Case of Amoebic Hepatic Abscess and Associated Pericarditis, Tr. Roy. Soc. Trop. Med. & Hyg. **31**: 689 (April) 1938.

4. Laigret, L.: Péricardite au cours d'une dysenterie amibienne, Bull. Soc. path. exot. **21**: 753, 1928.

ULCERATIVE TRACHEOBRONCHITIS FOLLOWING ATYPICAL PNEUMONIA

REPORT OF CASES

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It is no longer felt that atypical (viral) pneumonia is always as innocuous as it was originally described. Many patients have experienced recurring episodes of this disease over a period of several years. In some the symptoms have continued unabated; a productive cough has developed, and the presence of bronchiectasis has been confirmed by bronchographic examination. Other patients have had residual ulcerative tracheobronchitis associated with hemoptysis and production of sputum. These patients may show roentgenographic evidence of bronchial and bronchiolar dilatation and occlusion, atelectasis or obstructive emphysema. In others the convalescence has been prolonged and characterized by neurasthenia, chronic cough, production of sputum, pain in the chest, generalized weakness, easy fatigability, occasional hemoptysis, loss of weight or failure to regain previous weight lost, elevated sedimentation rate and low grade fever.

Twenty-nine of 150 patients having bronchoscopic examinations during the first six months of 1944 were found to have ulcerative lesions of the tracheobronchial tree. Nine of these patients had previous episodes of atypical pneumonia. Of the others, 6 had the lesions secondary to tuberculosis; 4 had them secondary to bronchiectasis, and in 3 they were associated with pulmonary abscesses. One had blastomycosis and 1 Boeck's sarcoid, and for 5 the cause of the lesions could not be determined. It is with the 9 patients whose ulcerative tracheobronchitis appeared to be secondary to previous attacks of atypical pneumonia that this paper is primarily concerned.

Atypical pneumonia is generally believed to be due to viral infection, though many pathogenic agents have been shown clinically and roentgenologically to be capable of producing this disease picture. Because of the difficulty in performing viral studies, the diagnosis must usually be made by exclusion, based primarily on the clinical course and the roentgenographic characteristics after the other etiologic agents have been eliminated.

Atypical pneumonia in its mild form has been frequently described.[1] Lately, other observers [2] have described a more severe, protracted and recurrent form of the disease occurring along with the milder forms in the same epidemic. The course may be longer, persisting in some in-

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1. (*a*) Haight, W. L., and Trolinger, J. H.: Primary Atypical Pneumania, Etiology Unknown, U. S. Nav. M. Bull. **41**:988-1000 (July) 1942. (*b*) Dingle, J. H.; Abernethy, T. J.; Badger, G. F.; Buddingh, G. J.; Teller, A. E.; Langmuir, A. D.; Ruegsegger, J. M., and Wood, B. W.: Primary Atypical Pneumonia, Etiology Unknown, War Med. **3**:223-248 (March) 1943. (*c*) Zimmerman, J. J.: Viral Pneumonia, Am. J. Nursing **43**:141-144 (Feb.) 1943. (*d*) Smiley, D. J.; Showacre, E. C.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis: A New Disease Entity, J. A. M. A. **112**:1901-1904 (May 13) 1939. (*e*) Murray, M. E., Jr.: Atypical Bronchopneumonia of Unknown Origin, New England J. Med. **222**:565-573 (April 4) 1940. (*f*) Suttenfield, F. D.: Primary Atypical Pneumonia (Virus Pneumonia), Mil. Surgeon **93**:360-364 (Oct.) 1943. (*g*) Grieco, E. H.; Cove, A. M., and Klein, E. C.: Pneumonia: A Survey of One Hundred and Six Cases, ibid. **93**:364-367 (Oct.) 1943. (*h*) McCarthy, P. V.: Primary Atypical Pneumonia of Unknown Etiology, Radiology **40**:344-346 (April) 1943.

2. (*a*) van Ravenswaay, A. C.; Erickson, G. C.; Reh, E. P.; Siekierski, J. M.; Pottash, R. R., and Gumbiner, B.: Clinical Aspects of Primary Atypical Pneumonia, J. A. M. A. **124**:1-6 (Jan. 1) 1944. (*b*) Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: Disease Entity Probably Caused by a Filtrable Virus, ibid. **111**: 2377-2384 (Dec. 24) 1938. (*c*) Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonias, Arch. Int. Med. **70**:513-522 (Oct.) 1942. (*d*) Reimann, H. A.: Viral Pneumonias, Bull. New York Acad. Med. **19**:177-181 (March) 1943. (*e*) Kneeland, Y., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, Bull. Johns Hopkins Hosp. **67**: 229-268 (Oct.) 1940. (*f*) Correll, H. L., and Cowan, I. I.: Primary Atypical Pneumonia, U. S. Nav. M. Bull. **41**:980-987 (July) 1943. (*g*) Hufford, C. E., and Applebaum, A. A.: Atypical Pneumonia of Probable Virus Origin, Radiology **40**:351-359 (April) 1943. (*h*) Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X), Bull. Johns Hopkins Hosp. **67**:268-305 (Oct.) 1940. (*i*) Smiley and others.[1d] (*j*) Grieco, Cove and Klein.[1g]

stances for months and occasionally being followed by complications. Van Ravenswaay and his associates [2a] have stressed the virulent aspect of this disease: Twenty-three and three-tenths per cent of their patients allowed to get up too soon had a recurrence of the pneumonia, and an additional 18.5 per cent had other complications, such as pleural fluid, empyema, chronic bronchitis and bronchiectasis. In my series there have been 20 patients in whom bronchiectasis developed after atypical pneumonia; 11 have had empyemas, and 9 have had residual ulcerative tracheobronchitis. Many others have had a delayed convalescence, characterized by neurasthenia, loss of weight, easy fatigability and chronic bronchitis. It is impossible to determine the general incidence of complications, for most patients were transferred to this hospital after the complications developed.

In a previous report [3] it was shown that atypical pneumonia may cause bronchial and bronchiolar infection and occlusion. The bronchial occlusion, manifested by areas of atelectasis, was demonstrated bronchoscopically by swollen, edematous and ulcerated mucous membrane, as well as by plugs of purulent exudate. Although ulcerations of the tracheobronchial tree have been shown microscopically in patients who died of atypical pneumonia, it is not generally realized in clinical practice that atypical pneumonia may be associated with or followed by ulcerative tracheobronchitis, recognizable bronchoscopically. This condition may account for the delayed convalescence, the symptoms of chronic bronchitis and hemoptysis and the recurring episodes of the disease noted in many patients. Roentgenologically, evidence of bronchiectasis, atelectasis or obstructive emphysema may be noted, depending on the duration, severity and degree of healing of the disease process. For other patients the roentgenogram of the chest may be normal.

Bronchoscopic examination of a patient with atypical pneumonia by Clerf, as reported by Reimann, showed diffuse inflammation of the entire tracheobronchial tree, particularly of the bronchus of the lower lobe of the left lung, which contained tenacious exudate. Dingle and his associates [1b] described the bronchoscopic observations in 10 patients with atypical pneumonia. There was an acute inflammatory reaction of the bronchial mucosa, with considerable congestion. The secretion was mucoid to mucopurulent. According to Blades and Dugan,[4] the appearance of the bronchial tree in a person with pseudobronchiectasis after atypical pneumonia is characterized by an extremely edematous mucous membrane, with a generalized inflammatory reaction which might be described grossly as suppurative bronchitis. It has not been my privilege to perform bronchoscopic examinations on many patients during the initial acute episode of atypical pneumonia. Those who have been so examined have shown diffuse inflammation of the mucous membrane, involving the larynx, trachea and both bronchial trees. The majority of patients with ulcerative tracheobronchitis have been transferred to this hospital several months after the onset of the disease and occasionally as long as six months to a year and a half afterward.

Bronchoscopic examination of patients with ulcerative tracheobronchitis following atypical pneumonia reveals the mucous membrane of the larynx, trachea and both bronchial trees to be severely inflamed and irritated. If the process is relatively acute, the mucous membrane is easily traumatized. The ulcerations are usually multiple and may be bilateral. The posterior and posterolateral walls are the sites usually involved, but the anterior wall may also be involved to a lesser extent. The ulcerations simulate the "tear drop" ulcer commonly found in tuberculosis, for which they could easily be mistaken. Occasionally the edges of the ulcer are ragged and hyperplastic. This hyperplasia could cause bronchial occlusion and atelectasis if the ulcer were located near a bronchial orifice. Usually, however, the borders of the ulcers are smooth, with only a little overhanging edge. The ulcers may be covered by a thin transparent grayish yellow membrane. Cultures of materials taken from such ulcers have not contributed to the diagnosis, only the usual bacterial flora being obtained. Facilities have not allowed viral studies. Biopsy of the ulcers and surrounding tissues has revealed nonspecific granulation tissue and inflammation. If the process is of long duration, it may be associated with scarring and stenosis of the secondary bronchial orifices, giving rise to obstructive emphysema and atelectasis. The ulcers are readily cauterized with 30 per cent solution of silver nitrate, whereas the intervening mucous membrane remains unchanged. The ulcerations tend to remain chronic and resistant to therapy. Healing usually takes place within a period of two to four months.

Diagnosis.—The diagnosis depends on the detection of ulcerations in the tracheobronchial tree in a patient who has or has had atypical pneumonia and residual symptoms therefrom. The patient may have a chronic productive bron-

3. Kay, E. B.: Bronchiectasis Following Atypical Pneumonia, Arch. Int. Med. **75**:89-104 (Feb.) 1945.

4. Blades, B., and Dugan, D. J.: Pseudo Bronchiectasis Following Atypical Pneumonia, Bull. U. S. Army M. Dept., November 1943, no. 70, pp. 60-68.

chitis with hemoptysis and recurrent episodes of pneumonitis or nonresolution of pneumonitis with roentgenographic or bronchographic evidence of bronchial or bronchiolar damage. Since it is frequently impossible to make a positive diagnosis as to the cause of the ulcers because of the difficulty in performing viral studies, this diagnosis must remain a clinical one, made after other etiologic agents capable of producing tracheobronchial ulcerations have been thoroughly investigated and excluded. So far, cultures of intrabronchial materials and biopsy have not aided. High titers of cold agglutinins in the serum have been of presumptive value. Tracheobronchial ulcerations secondary to chronic infective granulomas, particularly to tuberculous granulomas, have been the most difficult to differentiate bronchoscopically.

Differential Diagnosis.—Ulcerative tracheobronchitis associated with atypical (viral) pneumonia may be indistinguishable bronchoscopically from similar superficial ulcerations due to Boeck's sarcoid (fig. 1 *A*), from the chronic infective granulomas (fig. 1 *B*) or from the bronchomycoses (fig. 1 *C*). Bacteriologic and pathologic investigation in these diseases, however, has usually proved the cause. Early or superficial ulcerative tuberculous tracheobronchitis most closely simulates this condition bronchoscopically, although it tends to be even more

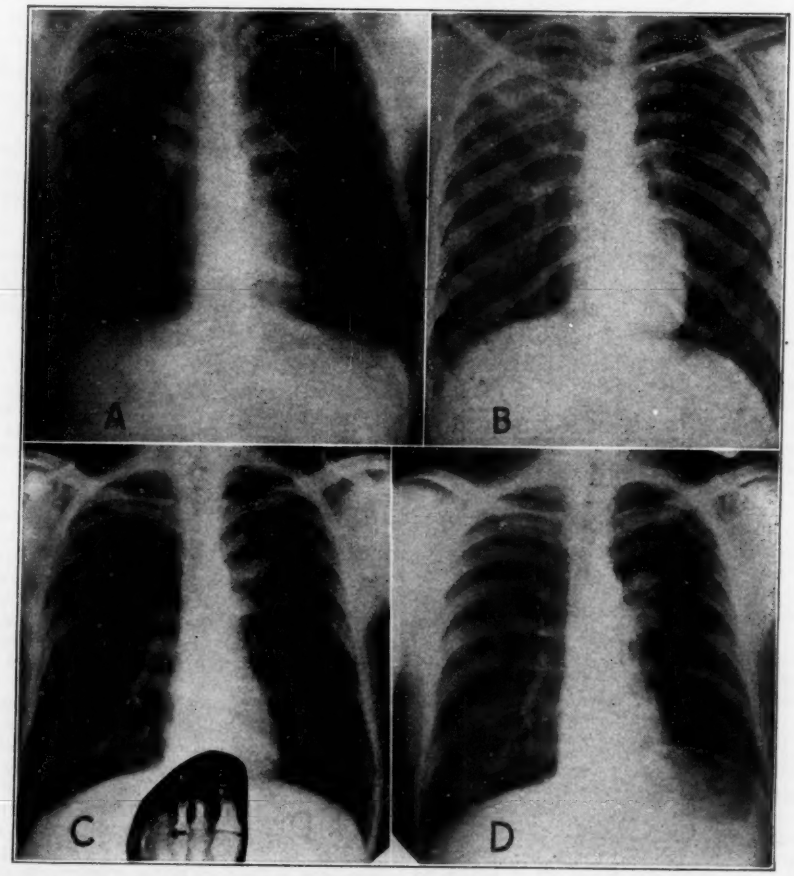

Fig. 1.—Roentgenograms of patients with other bronchopulmonary diseases who also had ulcerative lesions of the bronchi simulating those seen bronchoscopically in atypical pneumonia. *A*, involvement of the pulmonary and hilar lymph nodes seen in Boeck's sarcoid. There was pathologic verification of the diagnosis by examination of the lymph nodes by biopsy and by bronchoscopic biopsy. *B*, pulmonary tuberculosis of the apex of the right lung; acid-fast tubercle bacilli were obtained from the sputum. *C* and *D*, pulmonary and osseous involvement resulting from blastomycosis; *D* illustrates the appearance of the chest six months after *C* was taken, showing the definite improvement. The patient had a temporary interruption of the left phrenic nerve and removal of the fourth metatarsal bone and the proximal phalanx. He was given sulfonamide drugs for three months and was discharged clinically well.

chronic and resistant to therapy. Careful search for the tubercle bacillus by repeated cultures and inoculations in guinea pigs of sputum and gastric washings results in a positive diagnosis for a high percentage of tuberculous patients. The nonspecific inflammations and pyogenic ulcerations associated with bronchiectasis and pulmonary abscesses can readily be differentiated by the clinical course of these diseases.

Treatment.—A general hygenic regimen is followed. The patient is given complete rest in bed except for bathroom privileges, a high vitamin, high caloric diet and inhalations of steam or benzoin. If there is a productive cough, postural drainage is employed. The patient is examined bronchoscopically every four weeks, at which times the bronchial orifices of the secondary bronchi are sponged with tetracaine and epinephrine hydrochlorides solution to improve drainage and the ulcerations are cauterized with 30 per cent silver nitrate. The daily instillation of 3 to 5 cc. of penicillin (250 units to the cubic centimeter) into the tracheobronchial tree was thought to be of definite value in promoting more rapid healing. In subsequent cases, the concentration of penicillin has been increased to 10,000 units to the cubic centimeter, with evidence of further benefit. After a period of approximately one or two months of this regimen, the patient usually gains weight; the cough decreases or disappears, and a sense of well-being is noted. When the lesions appear bronchoscopically to be healing and the sedimentation rate becomes or remains normal, the patient is gradually allowed

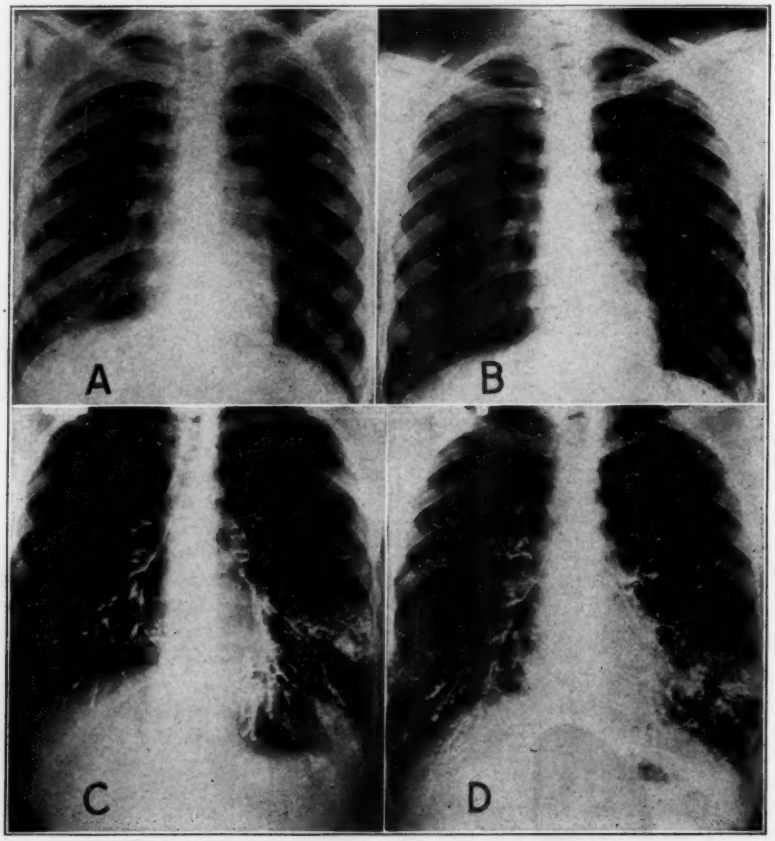

Fig. 2 (case 1).—Roentgenograms of a patient with recurring attacks of atypical (viral) pneumonia, ulcerative bronchitis and cylindric bronchiectasis of the lower lobe of the left lung. *A*, roentgenographic evidence of pneumonitis in the lower field of the right lung during the initial attack of atypical pneumonia Jan. 18, 1943. *B*, roentgenographic evidence of pneumonitis in the lower field of the left lung during a recurrent episode of atypical pneumonia Jan. 4, 1944. *C*, bronchogram made June 4, demonstrating minimal cylindric bronchiectasis in the lower lobe of the left lung. *D*, bronchogram made August 8, demonstrating no appreciable improvement in the bronchial dilatation even though there was considerable improvement in the ulcerative bronchitis shown bronchoscopically.

more activity but continues to have midmorning and midafternoon rest periods until complete healing has taken place. The ulcerations are usually healed within two to four months.

REPORT OF CASES

Only 4 reports of cases will be presented. These are characteristic of the group as a whole and illustrate the various clinical, roentgenographic and bronchoscopic aspects of the disease. All of the patients in these cases had two to four previous episodes of atypical pneumonia, which were all followed by chronic productive bronchitis and general debility. Three patients noted hemoptyses. The first case report illustrates migratory atypical pneumonia followed by bilateral ulcerative tracheobronchitis and bronchographic evidence of cylindric bronchial dilatation. The second is similar but emphasizes atelectasis. The third describes the complications of bronchostenosis and obstructive emphysema. The fourth demonstrates ulcerative bronchitis with no roentgenographic evidence of pulmonary residua.

CASE 1.—The patient, a 20 year old white youth, complained of a constant productive cough, loss of weight and nervousness. The past history was noncontributory. During childhood he had had scarlet fever, mumps, measles, whooping cough and chickenpox. The patient's health prior to his induction into the army was good. Two weeks after induction, Jan. 18, 1943, he contracted atypical pneumonia in the lower lobe of the right lung, characterized by chills, a temperature of 104 F., a productive cough and substernal pain. The white blood cell count was normal, and examination of the sputum showed only the normal flora. Physical examination revealed nasopharyngitis and rales in the right lower pulmonary field posteriorly. There was roentgenographic evidence of basilar pneumonitis on the right side (fig. 2*A*). The temperature was normal in five days, but the cough, sputum and general weakness persisted.

After eight weeks' hospitalization the patient was discharged to duty. He continued to have a cough and to raise sputum, but the symptoms were not sufficient to require his hospitalization. On October 29 the patient was rehospitalized for bilateral basilar pneumonitis, demonstrated by clinical and roentgenographic examination. The productive cough and substernal pain increased. His temperature at this time never went over 101 F. The sedimentation rate was 22 mm. in sixty minutes, and the white blood cell count was 6,100. The rales disappeared after three days, and within twelve days the chest was clear roentgenologically.

After four more weeks the patient was again returned to duty. The cough, sputum and general weakness continued. On Jan. 4, 1944, the patient again experienced an increase in the cough and sputum and complained of pain in the left side of his chest and was rehospitalized. The temperature was 103.4 F., the white blood cell count 7,800 and the sedimentation rate 26 mm. in sixty minutes. The throat was injected, and there were numerous coarse rales throughout the lower posterior field of the left lung. Roentgenograms showed pneumonia in the left base (fig. 2*B*). By January the pulmonary fields were again clear. He returned to duty March 23.

In May there was a fourth recurrence of the pneumonia, as before in the lower fields of the left lung, and he was transferred to Percy Jones General Hospital. Physical examination revealed moist rales throughout both pulmonary fields, more predominant on the left side. The patient showed evidence of loss of weight and general debility. There was a low grade elevation of temperature, up to 99.4 F., daily. The patient complained of substernal pain and pain throughout both sides of his chest. He had a persistent cough and raised between 20 and 30 cc. of purulent sputum daily. Smear, culture and inoculations in guinea pigs showed no growth of tubercle bacilli but did grow hemolytic streptococci and nonhemolytic Staphylococcus aureus. The white blood cell count was 6,600 and the sedimentation rate 29 mm. in sixty minutes. Cold agglutinins were present in a titer of 1 to 128. Because of the suggestive evidence of bronchiectasis, a bronchogram was made June 4, which showed cylindric bronchiectasis in the lower lobe of the left lung and several areas of bronchial dilatation in the lower lobe of the right lung, as demonstrated in figure 2*C*. Bronchoscopic examination on June 27 showed diffuse inflammatory hyperemia of the larynx, trachea and both main bronchi. Throughout the entire left main bronchus and, to a lesser extent, in the right main bronchus were multiple areas of superficial ulcerations, some of which had the "tear drop" appearance while others appeared shaggy and hyperplastic.

The ulcerations were thoroughly cauterized with 30 per cent silver nitrate solution. After this procedure the patient was treated as outlined in the section on treatment. The cough gradually decreased, as well as the production of sputum. The sedimentation rate by August 8 had decreased to 7 mm. in one hour. Rales persisted throughout both pulmonary fields, predominantly on the left, until August 1. Bronchoscopic examination August 21 showed definite improvement in the degree and extent of the ulcerative tracheobronchitis, that on the right side being almost entirely healed and that on the left side considerably improved. Bronchographic examination August 8 (fig. 2*D*) showed no significant improvement of the cylindric bronchial dilatation.

A gain in weight and a sense of well-being have been noted. The productive cough is noticeably improved but is occasionally present. The sputum now does not exceed 5 cc. in amount daily.

CASE 2.—The patient, a 51 year old officer, was hospitalized elsewhere for two weeks in November 1943 for an infection of the upper respiratory tract. The past history was entirely noncontributory. There were few symptoms referable to the lungs. A roentgenogram of the chest taken November 9 showed massive atelectasis of the lower lobe of the right lung, with an elevated diaphragm and mediastinal shift. By November 16 there had been spontaneous clearing of the lobar atelectasis. It was felt that the patient had had a mild attack of atypical pneumonia.

The patient was returned to duty and felt entirely well until December 19, at which time a productive cough developed and he was again hospitalized. There were 4 or 5 ounces (120 or 150 cc.) of purulent sputum daily. The temperature was elevated to 104 F. for four days and gradually fell by lysis. Atelectasis of the lower lobe of the right lung was again noted (fig. 3*A*), and a new pneumonic process had developed in the base of the left lung. Also, there was an increase in the obliterative pleuritis, resulting in elevation and flattening of the left side of the diaphragm. Within a week, as before, there was spontaneous clearing of the atelectasis, but the process in the lower lobe of the left lung persisted for

the next month (fig. 3 *B*), associated with basilar rales on this side. The productive cough disappeared.

The patient was then transferred to Percy Jones General Hospital. Bronchoscopic examination performed Jan. 24, 1944, showed erythematous granular mucous membrane with several small superficial areas of ulceration in the bronchus of the lower lobe of the left lung, while the bronchus of the lower lobe of the right lung showed extensive ulceration of an acute nature, with some diminution of the bronchial lumen. The bronchial ulcerations were thoroughly cauterized with 30 per cent silver nitrate solution. Because of the suggestive evidence of bronchiectasis, bronchographic examination was performed January 31, and damaged, dilated and somewhat distorted bronchi and bronchioli were noted in the bronchograms (fig. 3 *C*). The patient was treated according to the procedure previously outlined. A second bronchoscopic examination, on March 11, showed complete healing of the previous ulcerative bronchitis. However, bronchographic examination March 21 (fig. 3 *D*) showed a slight increase in the bronchial dilatation.

Additional bronchograms obtained later showed this process to be stationary.

Case 3.—The patient, a 25 year old man, was hospitalized elsewhere Feb. 17, 1943, for atypical pneumonia, characterized by fever, cough and generalized weakness of two days' duration. The past history was noncontributory. His temperature on his admission to the hospital was 103.4 F. The white blood cell count was 5,000, with a differential count of 65 per cent polymorphonuclear leukocytes, 27 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. The patient appeared extremely ill and was dyspneic, and rales could be heard in the right lower pulmonary fields posteriorly. A roentgenogram revealed pneumonic infiltration at the base of the right lung. Treatment with sulfadiazine was started immediately but was discontinued after three days because of no alleviation of the fever.

By March 3 there were rales throughout both pulmonary fields. Roentgenographic examination at this time showed patchy areas of pneumonitis throughout the right lung and in the left hilar region (fig. 4 *A*). Dyspnea and cyanosis were so severe as to require oxygen therapy. There was only a moderate amount of sputum, and this was negative for pathogenic organisms, including tubercle bacilli. There was hemoptysis on one occasion. Clinical and roentgenographic examination of the chest showed clearing of the multiple areas of pneumonia, except for those in the base of the right lung, by April 19 (fig. 4 *B*), and these were clear by May 6.

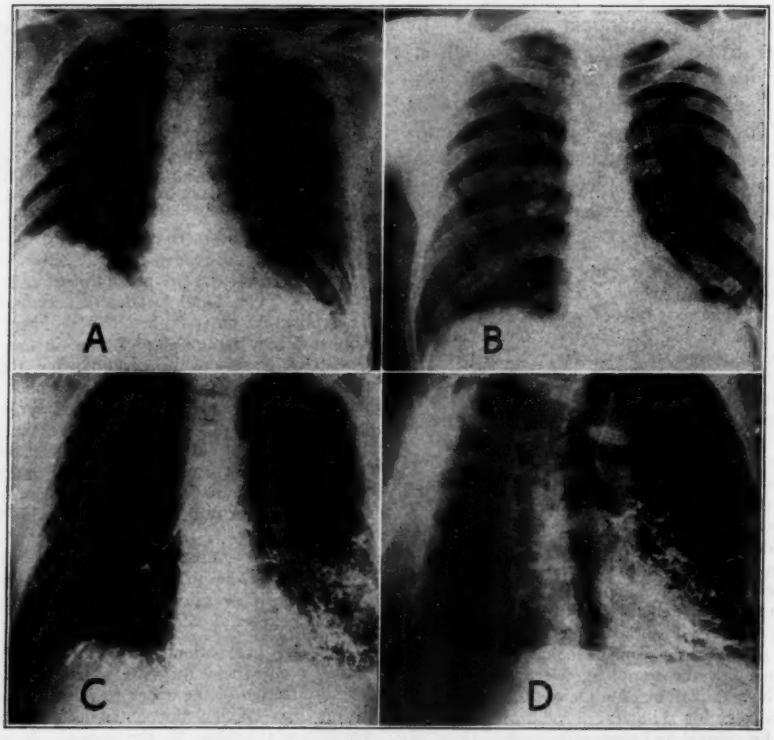

Fig. 3 (case 2).—Roentgenograms of a patient who had two attacks of atypical pneumonia associated with ulcerative bronchitis, atelectasis of the lower lobe of the right lung and residual bronchial damage of the lower lobe of the left lung. *A*, evidence of the elevated right side of the diaphragm associated with atelectasis in the base of the right lung and pneumonitis in the base of the left lung Dec. 19, 1943; *B*, roentgenogram made December 26, demonstrating spontaneous clearing of the atelectasis of the lower lobe of the right lung but some increase in the pneumonitis in the left lower pulmonary field; *C*, bronchogram made Jan. 31, 1944, demonstrating dilated and distorted bronchi of the lower lobe of the left lung; *D*, bronchogram made March 21, demonstrating slight increase in the bronchial dilatation. The ulcerative bronchitis appeared bronchoscopically to be healed at this time.

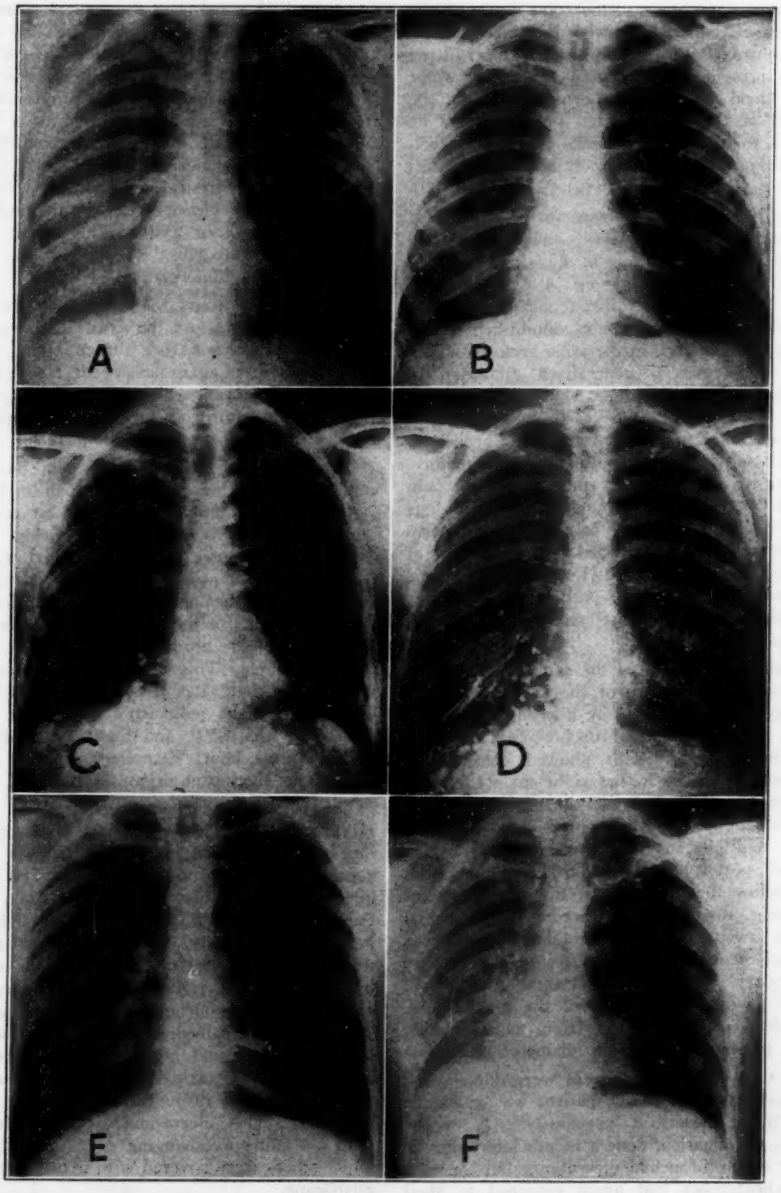

Fig. 4 (case 3).—Roentgenograms of a patient with recurring attacks of atypical pneumonia, bronchoscopic evidence of ulcerative tracheobronchitis, with multiple sites of bronchostenosis on the right side and residual obstructive emphysema of the right lung. *A*, roentgenographic evidence of bilateral pneumonitis during the initial episode of atypical pneumonia March 3, 1943; mediastinal shift to the right side is noted. *B*, roentgenogram made April 19, showing clearing of the bilateral pneumonitis except in the base of the right lung. Mediastinal shift to this side is still present. *C*, roentgenogram taken Jan. 18, 1944, showing evidence of emphysema of the right lung. *D*, bronchogram taken April 15, demonstrating generalized tubular dilatation of the smaller bronchi of the right lung, with apparent occlusion of the terminal ends proximal to the emphysema; this was interpreted to be due to inflammation, mucous plugs or scarring and resulted in a ball valve mechanism accounting for the emphysema. *E* and *F*, roentgenograms demonstrating obstructive emphysema of the left lung in another patient having ulcerative bronchitis with multiple sites of bronchostenosis, as did the patient whose bronchogram is shown in *D*, but no definite evidence of previous attacks of atypical pneumonia.

The patient then returned to duty but noted a chronic moderately productive cough and weakness. On July 26 he was again hospitalized for a productive cough, dyspnea on exertion and pain in the right aspect of the chest. Physical examination showed diminished breath sounds and resonance over the entire right aspect of the chest and the presence of a friction rub in the right axilla. The blood count was normal, as was the roentgenogram of the chest. After several weeks he again returned to duty and remained moderately well except for the productive cough, dyspnea and weakness.

On Jan. 18, 1944, the patient was again hospitalized for what was diagnosed as a "cold" and fever of two days' duration. Roentgenograms at this time revealed emphysema of the right lung (fig. 4 *C*). Physical examination revealed rales throughout the right pulmonary field and the presence of diminished breath sounds and hyper-resonance in the same area. Bronchograms (fig. 4*D*) revealed generalized dilatation of the smaller bronchi on the right side with apparent occlusion of the terminal ends. This prevented the iodized poppyseed oil from entering the distal bronchioli and alveoli. Those that did fill appeared emphysematous. The occlusion of the terminal ends of the bronchi was presumed to be due to inflammation, mucous plugs or scarring. Apparently a ball valve mechanism had resulted from the disease process. A diagnosis of emphysema of the middle and lower lobes of the right lung secondary to atypical pneumonia was made, and the patient was then transferred to Percy Jones General Hospital.

Physical examination showed the same conditions as those just described. Because of the previous history of atypical pneumonia followed by a productive cough and evidence of emphysema, bronchoscopic examination was done May 19. This showed considerable tenacious mucous exudate in the right main bronchus and about the bronchial orifices; the surfaces of the mucous membranes were hyperemic and inflamed. There were multiple superficial ulcerations on the posterior and posterolateral walls, extending from 1 to 2 cm. below the bronchus of the upper lobe of the right lung down to the secondary bronchial orifices of the lower lobe of the right lung. There was definite partial stenosis of the orifices of the bronchi of the secondary, mediastinal, vertebral and dorsal lobe, as well as of the bronchus of the middle lobe. These bronchial orifices varied from approximately the size of a pinpoint to 2 mm. in diameter.

All of the sites of bronchostenoses were dilated, and the ulcers were cauterized. The patient was given the general treatment described previously. A second bronchoscopic examination, done a month later, showed some healing of the bronchial ulcerations, but the sites of the bronchostenoses had again returned to their previous caliber. During the interim there was some decrease in the cough and the production of sputum but no apparent change in the roentgenographic and clinical evidence of emphysema. The patient was discharged from the army before further therapy could be carried out.

Figures 4 *E* and 4 *F* show the roentgenograms of another patient who had more pronounced evidence of obstructive emphysema and also bronchoscopic evidence of ulcerative bronchitis and multiple sites of bronchostenosis of the secondary bronchi similar to those of the patient described.

CASE 4.—The patient, a 36 year old medical officer, was admitted to Percy Jones General Hospital July 21, 1944, with the history of bilateral atypical pneumonia in 1941 which had the typical roentgenographic appearance and clinical course. This had cleared after four to six weeks without residua. In childhood the patient had had mumps, smallpox, chickenpox and whooping cough. He remained healthy until April 1944, at which time he was hospitalized for a "chest cold" associated with chills, a temperature of 101.4, headache and pain in the right side of the chest and the substernal areas. Physical examination revealed nasopharyngitis and evidence of rales in the right pulmonary field in the posterior axillary line at the level of the seventh and eighth ribs. Roentgenograms of the chest showed nothing abnormal.

In forty-eight hours the rales had disappeared; the patient felt well, and he was discharged to duty. Within three days a sore throat, cough, sputum and a low grade fever again developed. He was hospitalized for one week, during which time thorough examinations of the sputum for pyogenic organisms, tubercle bacilli and coccidioides were made without result.

On June 2 the patient was again hospitalized for chills, a temperature of 101.4 and pain in the right side of the chest. Examination of the chest revealed coarse rales throughout both pulmonary fields. Within two days the temperature was again normal and the patient felt better, but a productive cough developed that was associated with hemoptysis on three or four occasions. Roentgenograms of the chest showed evidence of pneumonitis in the right cardiophrenic angle of the right pulmonary field. This gradually disappeared over two weeks' time, but rales persisted posteriorly and laterally in the right pulmonary field. The white blood cell count was 4,500, and the sedimentation rate was 31 mm. in one hour. Examination of the sputum again showed no significant organisms.

The patient was then transferred to Percy Jones Hospital. There was definite evidence of chronic illness, characterized by general debility, nervousness, a productive cough and hoarseness. The pharynx was injected. Examination of the chest again revealed the presence of inspiratory rales in the right pulmonary field posterolaterally. Roentgenograms of the chest were normal. Because of the previous experience of finding ulcerative tracheobronchitis following atypical pneumonia, a bronchoscopic examination was done July 27. An inflamed, irritated mucous surface of the larynx, trachea and both bronchial trees was noted. Beginning at the carina on the right side were extensive ulcerations throughout the entire right main bronchus. The ulcerations were moderately deep, with a slightly overhanging edge. Some appeared red, while others were covered with a transparent yellowish membrane.

The ulcers were examined by culture and biopsy and were cauterized with 30 per cent silver nitrate solution. No pathogenic organisms were grown on culture. Facilities were not available for viral studies. The microscopic examination of the tissue showed only nonspecific inflammation. Extensive studies for both tuberculosis and fungous infections were done without result. The white blood cell count remained normal, but the sedimentation rate decreased to 7 mm. in sixty minutes. There was no evidence of cold agglutination. The patient was given rest in bed for a month, a high vitamin, high caloric diet with supplementary

vitamins and frequent steam inhalations. Daily intratracheal instillation of penicillin was done. The patient gradually improved; the cough, sputum and hoarseness disappeared, and there was an increase in appetite and a gain of 10 pounds (4.5 Kg.) in weight.

On September 3 a second bronchoscopic examination was done, which showed normal-appearing mucous membrane of the larynx, trachea and bronchi. There was practically complete healing of the ulcerative bronchitis except for one small patch, approximately 12 by 4 mm., on the left posterolateral wall of the right main bronchus.

SUMMARY

Atypical (viral) pneumonia in its more protracted and recurrent form was studied. This disease may be complicated by bronchiectasis, empyema, ulcerative tracheobronchitis and delayed convalescence. Patients with atypical pneumonia may have ulcerative lesions in the tracheobronchial tree, and these may be responsible for the protracted and recurrent forms of this disease. Bronchoscopic examination is indicated in the management of such patients, for both diagnosis and local therapy. General hygienic therapeutic measures directed to the patient are important. It is felt that the daily instillation of penicillin intratracheally has been of value in promoting more rapid healing of the tracheobronchial ulcerations.

EPIDEMIC HEPATITIS WITH AND WITHOUT JAUNDICE

SOME CLINICAL STUDIES ON TWO HUNDRED AND FIFTY-FIVE PATIENTS AMONG TROOPS IN A COMBAT ZONE

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In almost every war during the last one hundred and fifty years increased numbers of cases of jaundice have been observed among soldiers. According to a report in The Bulletin of the U. S. Army Medical Department,[1] "There were 22,569 cases and 161 deaths during the Civil War in a total of 2,218,559 troops; the disease occurred in troops during the Boer War, the War of 1812, the Spanish-American War, and World War I." Similar outbreaks were experienced by British troops in the Middle East in 1941 and 1942. During the late summer and fall of 1943 an epidemic of infectious hepatitis began among American, British and French troops in the North African theater. Admissions to the hospital for jaundice in this theater, which included Sicily and Italy, began to increase in August and September, reached a peak during the winter months and then began to decline. This increasing incidence of hepatitis presented an unusual opportunity to study the clinical characteristics of a large number of these cases and to compare them with those seen in various other types of jaundice.

METHODS AND MATERIAL

During the six month period from Nov. 16, 1943 to May 16, 1944, a total of 448 patients with jaundice were admitted to the gastroenterologic service of a general hospital located in Italy. Many additional patients were admitted to other medical wards, or jaundice developed in patients in the surgical wards; hence this figure is not a true index of the number of patients admitted to this hospital during this period.

Of this total, 196 patients with hepatitis and jaundice uncomplicated by other diseases and 42 patients having additional diseases simultaneously were studied by means of various clinical and laboratory tests. This report is based on our observations of this group of 238 unselected patients with hepatitis and jaundice. In addition to these, 17 patients with hepatitis without jaundice were observed and similarly studied.

Because of the large number of patients under observation during a relatively short period, specimens of varying size were studied by different clinical and laboratory tests. In addition to a careful clinical history and physical examination, we studied some patients by weekly determinations of the icterus index, van den Bergh reaction, urinalysis, bile content of the stools and complete blood counts. Various special studies, such as the hippuric acid test of hepatic function according to the gravimetric method of Quick,[2] the sedimentation rate according to the method of Wintrobe and Landsberg,[3] the coagulation time by the capillary tube method,[4] the heterophile agglutination test and the dark field examination of blood and urine for leptospiras and spirochetes, were performed on a variable but significant number of patients. Examinations of urine and stools for bile were frequently made throughout the course of the disease on all patients. Each was frequently examined for any changes in physical conditions, with particular emphasis on the degree of icterus, lymphadenopathy, hepatic tenderness or enlargement and splenomegaly.

Those studied were patients with hepatitis consecutively admitted and unselected except that for purposes of study an icterus index of at least 16 was arbitrarily set as the lower limit indicating the presence of jaundice. A large number of patients with milder forms of the disease were thus excluded, but in the cases reported the diagnosis of epidemic hepatitis with jaundice has been unquestionably verified.

CLINICAL DATA

Age, Race and Sex.—The average age of the 101 patients was 23.9 years, the youngest being 19 and the oldest 38. All were white men. There were no Negroes in this series. Since the ratio of Negro troops to white troops in this theater is unknown, no conclusion as to this apparent racial immunity can be drawn. There were only 2 women admitted to this hospital with jaundice during the six month period of this study; however, less than 1 per cent of the patients admitted to the hospital during this period were women.

Incubation Period.—No accurate estimation of the incubation period could be made because of the lack of any history of known contacts for 28 per cent of the patients and because of the

1. Epidemic Hepatitis: A War Disease, Bull. U. S. Army M. Dept. November 1943, no. 70, p. 4.

2. Quick, A. J.: The Synthesis of Hippuric Acid: A New Test of Liver Function, Am. J. M. Sc. **185**:630 (May) 1933.

3. Wintrobe, M. M., and Landsberg, J. W.: A Standardized Technique for the Blood Sedimentation Test, Am. J. M. Sc. **189**:102 (Jan.) 1935.

4. Methods for Laboratory Technicians, U. S. War Department, Technical Manual 8-227, Washington, D. C., Government Printing Office, Oct. 17, 1941, p. 28.

extremely wide range of multiple contacts for the remaining 72 per cent. Cameron,[5] in his studies on 170 patients with epidemic hepatitis observed in Palestine in 1940 and 1941, stated the belief that the minimum incubation period was thirty-two days and in many cases much longer. We have not been able to add further information in regard to the incubation period.

For convenience of description we have separated the disease into three phases: preicteric, icteric and convalescent phases, and each will be discussed in detail.

Preicteric Stage.—These data were compiled from an analysis of 100 unselected case histories. The onset of the preicteric stage is variable but may be abrupt, with fever, chills, generalized myalgia and symptoms common to an infectious systemic disease.

Sixty-one per cent of our patients fall into this group having a moderately abrupt onset of the disease. The temperatures ranged from 99 to 104.6 F. for from one to seven days. The average duration of fever was three days, and 92 per cent of the patients were febrile for one to three days only. The temperature was usually relatively low and irregular and fell by lysis. In addition to this type of temperature curve, 3 patients had a low grade fever, with temperatures of 99 to 100 F., which recurred irregularly throughout the disease. In a few instances it would recur in a typically Pel-Ebstein type of curve, with an afebrile period of a week or ten days followed by a short interval of fever for one to three days. No other cause for the fever except the hepatitis could be ascertained in these patients. The vast majority did not exhibit this phenomenon, but in a small percentage it was a noteworthy feature.

In the remaining 39 per cent the onset was more insidious and was manifested by anorexia, nausea, vomiting, weakness, vague gastrointestinal symptoms or a dull aching in the right upper quadrant or both upper quadrants of the abdomen. No fever or chills were noted by this group. There was a slight tendency toward bradycardia during this stage, but this was rarely a striking feature.

During the preicteric stage 34 per cent of the patients had chilly sensations and an additional 29 per cent had definite rigors. Simultaneously with the chills and fever, 32 per cent had symptoms of a mild coryza, with nasal discharge or a nonproductive cough. Some stated they felt as if they had influenza, and 2 per cent had an associated sore throat. Early in the course of the disease, prior to the development of a definite jaundice, it was almost impossible to distinguish this stage from an early atypical pneumonia, influenza, nasopharyngitis or malaria.

Anorexia was the most important early differential diagnostic guide during this period. Although a frequent symptom of the other diseases mentioned, it was not usually so severe and well defined as it was in patients with epidemic hepatitis. Almost from the onset, usually during the first few days, anorexia became the outstanding single symptom and was present in 87 per cent of the patients. This was frequently associated with nausea, which was an important early symptom in 84 per cent of the patients, Not infrequently even the sight or smell of food was sufficient to produce this complaint.

Although anorexia and nausea were frequent, vomiting was noted in only 51 per cent, and this was never severe at this stage or subsequently in the majority of the patients studied.

Pruritus was unusual during the preicteric phase but was subsequently noted in varying degrees of severity by 39 per cent of the patients. In only 2 patients was the pruritus severe or troublesome.

Diarrhea, usually mild, with three to four loose, watery stools without blood, pus or mucus, occurred in 33 per cent during the preicteric or early icteric phase of the disease. This contrasts with the 22 per cent in whom a tendency toward constipation developed. Diarrhea was also encountered frequently in the late icteric stage, during the transition from a low fat diet to a regular diet. At this time a few loose stools were frequently noted.

Other symptoms developed during this period. One was a sense of fulness in the epigastrium or right and left upper quadrants of the abdomen. An ache high in the back opposite the liver and spleen associated with a dull ache in the hepatic area anteriorly is common. This was usually described as a "dull hurting" which was frequently worse at night or with riding over rough roads in an army vehicle. At times, with jarring it became severe and sharp and was referred to the right shoulder.

"Heart burn," transitory dizziness, weakness, easy fatigability, headache (usually frontal or behind the eyes) and pains in the joints without objective redness, swelling or increased heat were frequently encountered in the early stage. The average duration of the preicteric stage was four and seven-tenths days. The frequency of the various symptoms in epidemic hepatitis is shown in table 1.

During the latter part of the preicteric stage the disease pursued one of two courses: Either it

5. Epidemic Hepatitis or Catarrhal Jaundice, editorial, J. A. M. A. **123**: 636 (Nov. 6) 1943.

remained so mild that jaundice never developed, or the patient rapidly became deeply or moderately icteric.

Icteric Stage.—The transition from the preicteric stage to that of a definite icterus was characterized by the appearance of dark amber urine and jaundice. The jaundice usually followed the febrile period but occasionally developed simultaneously with the fever. The average time for jaundice to appear was four and seven-tenths days after the onset of fever but varied from one day to as long as several weeks. The duration of the icterus was variable, ranging from sixteen days to seven or more months. The average time for the icterus index to remain abnormally high (over 12) was thirty-nine and two-tenths days.

The maximum degree of icterus was usually reached during the first two to three weeks; then it precipitously fell to a low elevated level, maintained a plateau at the slightly elevated level for several weeks and then gradually returned to normal. The rapidity of the fall in the icterus index and the concurrent relief of symptoms which accompanied it were frequently dramatic. This is illustrated in table 4. A rapid rise and fall of the icterus index was the rule in the majority of the patients. The rapid subsidence of jaundice, however, was one of the most misleading features of this disease, as the underlying hepatitis remained active and there was evidence of functional hepatic impairment both clinically and by the hippuric acid test long after the jaundice had subsided. These data are summarized later in this paper.

TABLE 1.—*Incidence of the Predominant Symptoms in One Hundred Patients with Epidemic Hepatitis*

Symptom	Incidence (Percentage)
Anorexia	87
Nausea	84
Chills and chilly sensations	63
{ Chills 29 { Chilly 34	
Fever	61
Vomiting	51
Pruritus	39
Myalgia	34
Diarrhea	33
Coryza (at onset)	30
Constipation	22
Sore throat (at onset)	2

There was no definite correlation between the degree of icterus and the severity of the hepatitis. Not infrequently some of the patients with an icterus index never higher than 18 throughout the course of the disease appeared sicker, and the course was more chronic than that of some who became deeply jaundiced and had an icterus index of over 100.

During this icteric stage, the patients' symptoms tended to subside rapidly but there might be frequent exacerbations with recurring enlargement and tenderness of the liver and occasionally a second or third rise in the icterus index. This tendency to relapse after the disease has apparently subsided is under certain conditions a characteristic feature of this type of hepatitis.

Convalescent Stage.—After the jaundice had initially subsided to a low elevated level, the period of convalescence began. This is an extremely important period in the treatment of this disease, and this stage was characterized by a tendency toward frequent relapses. The exact frequency of relapses in this series is unknown because of our inability to obtain adequate follow-up studies on the majority of the patients after they had been discharged from the hospital. Relapses while the patients were still in the hospital under observation were frequent enough for us to observe two precipitating factors.

Relapses were frequently observed in patients in whom an intercurrent infection of the respiratory tract developed. The severity of the relapse seemed to depend on the severity of the infection of the respiratory tract. In general this type of relapse was relatively mild, although associated with an exacerbation of the patient's symptoms, transitory hepatic enlargement and a rise in the icterus index. Frequently it was so transitory that the usual course of the disease was not greatly prolonged.

The second, and more severe, type of relapse was that which resulted from too much physical exertion prior to the time the hepatitis was completely cured. The amount of exertion necessary to produce this was variable, depending on the degree of healing of the hepatitis and the type of exertion. We have repeatedly seen an exacerbation follow the climbing of two flights of stairs or a short leisurely walk. Running, jumping and not infrequently simply riding in an army vehicle have been precipitating factors. The rigors of military life and the fatigue of actual combat conditions has been a definite factor in precipitating a relapse after the patient was considered well.

A recurrence resulting from fatigue was characterized by a dull ache in the region of the liver with an occasional sharp cutting pain which might be referred to the back or to the right shoulder. At times the pain in the region of the liver was severe and closely simulated that of acute chole-

cystitis. Rarely pain was experienced in both upper quadrants of the abdomen. Associated with this pain was a return of anorexia, nausea and vomiting, usually with an increase in the icterus index and biliuria. The liver usually enlarged and became palpable and tender. In an occasional patient the liver did not become palpable, but a transitory hepatomegaly was the rule during a relapse. There seemed to be some correlation between the degree of fatigue and the severity of the relapse. In general, the more fatigue experienced the more severe and prolonged the recurrence.

Those relapses which occurred in patients after a return to actual combat duty tended to be more severe than those developing in patients while they were in the hospital, and not infrequently they were more severe than the original attack. These patients required a prolonged recovery period, and in a small percentage a chronic hepatitis developed.

In an attempt to determine why these patients, who were seemingly well, tended to have an exacerbation on returning to even mild activity, various studies were made. In these studies it was found that the sedimentation rate was frequently markedly elevated for several weeks after the icterus index had returned to normal and that hepatic function, as measured by the synthesis of hippuric acid, was seriously impaired for as long as two months after the icterus index had returned to normal. The activity of the hepatitis and the functional inefficiency of the liver over such a period would seem to favor the development of relapses.

The rapid fall in the icterus index and the apparent rapid clinical improvement in these patients after treatment is started are treacherous, misleading and characteristic features of this type of hepatitis. Residual hepatic damage and activity of the hepatitis may persist for weeks or months after the icterus index has returned to normal. We feel that this residual activity and functional hepatic insufficiency are the basis for the tendency to relapse when the hepatitis has seemingly subsided.

It is important to realize that the hepatitis is not cured in the majority of patients when the icterus index returns to normal and the patient begins to feel well. If cautious, conservative treatment with the emphasis on rest in bed and adequate intake of fluids is insisted on for one or two weeks after the icterus index has returned to a normal level, we believe that most relapses can be avoided or minimized. If this is not done, relapses occur frequently and a chronic hepatitis may develop.

Physical Examination.—The incidence of physical findings in 200 patients with infectious hepatitis with jaundice is shown in table 2.

The degree of icterus varied from a faint tint of the scleras to an orange-bronze discoloration of the scleras and skin. A few of the patients were so deeply jaundiced that they had a dusky, cyanotic hue added to the deep yellow color of the skin.

Hepatic enlargement is a characteristic feature of this disease, and the liver was clinically palpable in 58 per cent of the patients. The degree of enlargement was at times striking and has been observed a full handbreath below the costal margin. An enlargement of 1 or 2 fingerbreadths below the right costal margin was the rule. Hepatic tenderness was also a common finding, being present in some degree in 66.5 per cent of the patients. The degree of tenderness varied from a mild sense of soreness to severe pain on deep palpation. In 33.5 per cent no tenderness was noted at any time throughout the course of the disease.

TABLE 2.—*Physical Findings in Two Hundred Patients with Epidemic Hepatitis with Jaundice*

Finding	Incidence (Percentage)
Icterus of skin	100
Icterus of scleras	100
Lymphadenopathy [6]	81
Axillary	70
Inguinal	54.5
Axillary and inguinal	33
Cervical	19
Generalized	15.5
Epitrochlear	6
Hepatic tenderness	66.5
Hepatic enlargement (palpable) [7]	58
Conjunctival injection	27
Mild	10
Moderate	15
Intense	2
Enlargement of spleen (palpable)	9
Injection of palate	5.5
Conjuctival hemorrhage	2
Dermatitis	2

Lymphadenopathy, present in some degree in 81 per cent of the patients, was frequently a striking feature. The lymph nodes ranged in

6. In evaluating the lymphadenopathy we carefully excluded all patients having abrasions, dermatitis, furuncles or other lesions that might have produced a similar enlargement of the nodes from a purely local cause. It is therefore felt that the lymphadenopathy is a characteristic feature of this disease.

7. A roentgenogram of the liver and spleen to determine the size of these organs was made in 31 cases, and both liver and spleen were found enlarged in 26 of the 31 cases. In 5 cases of hepatitis without icterus the roentgenogram has revealed both hepatic and splenic enlargement to be present.

size from that of a small pea to that of an English walnut. The size and consistency of the enlarged nodes varied with the different stages. During the early part of the disease, the nodes were frequently soft, mushy, freely movable, nontender and discrete; later they became firm, smaller and shotlike. There was no tendency toward suppuration or matting together. The axillary and inguinal nodes were most frequently involved. The frequency and location of the lymphadenopathy are listed in table 2.

The spleen was clinically palpable in 9 per cent of the patients. The splenomegaly was frequently transitory in the early stages or was found later in the more severely ill patients. In an attempt to evaluate this further, roentgenograms were made of the liver and spleen to determine the size of these organs in 31 patients at varying stages of the disease. The liver and spleen were found enlarged in 26 of the 31 patients thus studied. From this evidence it would seem that both hepatic and splenic enlargement are frequently encountered and are characteristic features of epidemic hepatitis.

Conjunctival injection, present in 27 per cent of the patients, is of interest in view of its reputed importance in the diagnosis of Weil's disease. The degree of injection was considered to be mild in 10 per cent, moderately severe in 15 per cent and severe in 2 per cent of the patients. The cause of the injection of the conjunctivas is unknown, but it is doubtful that it has any diagnostic significance. There was some tendency for the degree of injection to coincide with the degree of icterus. Those patients having the highest and most persistent icterus index tended to have the more severe conjunctival injection. Conjunctvial hemorrhages were noted in 2 per cent of the patients; these were small areas 1 to 3 mm. in diameter, located on the outer medial part of the bulbar conjunctiva. In none of these patients exhibiting conjunctival injection or hemorrhage was it possible to demonstrate any type of leptospiras in dark field examinations of either the blood or the urine.

Injection of the soft palate was noted in 5.5 per cent of the patients early in the preicteric stage of the disease, and, since a majority of the patients were admitted to the hospital after the development of jaundice, this may be a more frequent early observation.

A dermatitis of any type was rare, as only 5 of the 448 patients had any type of cutaneous rash at any time during the course of the hepatitis. In 3 of these there was a diffuse, macular erythematous rash over the abdomen, the anterior part of the chest and the upper extremities. This type of dermatitis was seen early in the disease shortly after or coincidental with the febrile period of the preicteric stage. The rash completely disappeared within three days in all cases.

In 1 patient a generalized urticaria developed, and another had a few petechiae during the icteric phase of the hepatitis. In none was the rash severe or troublesome.

LABORATORY STUDIES

Blood.—In an attempt to evaluate the effect of this illness on the blood, we studied a group of 100 patients by means of weekly blood counts throughout the course of the disease. A summary of these data is shown in table 3, which gives the average range of the white blood cell and differential counts at weekly intervals.

The average range of the white blood cell count was 7,149 to 9,975, but the actual range varied from a leukopenia of 2,700 to a leukocytosis of 38,600. It was unusual for the white

TABLE 3.—*Average Weekly White Blood Cell Count and Differential Count of One Hundred Patients with Epidemic Hepatitis*

Week	Initial	1st	2nd	3rd	4th	5th	6th
Polymorphonuclear Leukocytes	49.5	50.6	52.0	51.3	49.8	51.3	49.2
Lymphocytes	44.1	42.5	41.0	40.3	41.6	39.3	40.0
Mononuclear Leukocytes	3.2	3.7	3.0	3.9	3.7	5.0	6.5
Eosinophils	2.0	2.3	3.0	3.5	4.4	3.3	3.0
Basophils	1.2	0.9	1.0	1.0	0.5	1.1	1.3
White blood cell count	7,149	7,751	7,913	7,727	9,268	7,894	9,975

cell count to be over 12,000, and only 3 per cent of the patients in this group had a leukocyte count of over 12,000. The highest white blood cell count was noted in the patient who died and was probably a reflection of the severe complications which were observed in this patient. A leukopenia or a normal white blood cell count is considered to be more characteristic of the disease. The leukopenia is especially characteristic during the febrile or preicteric stage and shortly thereafter. There was a slight tendency in many of the patients for the white blood cell count to rise slowly to a high normal value or slight leukocytosis as the disease progressed throughout its course.

The differential white blood cell count usually showed a relative lymphocytosis throughout the disease, the percentage of lymphocytes being as high as 87 per cent of the white blood cells. In an occasional patient no increase in the relative number of lymphocytes was observed, but this was unusual.

There is little if any tendency toward the development of anemia in the average patient

without complications. In only 3 per cent of the 100 patients studied by repeated examination of the red blood cell counts, hemoglobin content and hematocrit values was any significant anemia noted. In 2 of these patients a mild, transitory anemia developed, which was unexplained and required no treatment. The third patient had repeated severe hemorrhages from a gastritis with large gastric ulcerations and subsequently died. Hemorrhage from gastrointestinal ulcerations, especially if accompanied with a prolonged prothombin time and coagulation time, may result in death. Hence it is felt that, although the tendency toward the development of anemia is relatively slight, one should be constantly on the alert for the development of an acute anemia secondary to hemorrhage from the gastrointestinal tract. This is the only significant type of anemia seen in this series and occurred only in the patient with a rapidly fatal course.

TABLE 4.—*Van den Bergh Reactions and Icterus Indexes of One Hundred Patients with Epidemic Hepatitis (by Week)*

Week of Disease	Direct (Percentage)	Biphasic (Percentage)	Indirect (Percentage)	Average Icterus Index (Units)
Initial	37	63	0	49.4
Second	33	66	1	28.1
Third	14	86	0	19.6
Fourth	2	95	3	16.6
Fifth	0	94	6	14.3
Sixth	0	100	0	14.1
Seventh	0	88	12	14.2

Icterus Index and van den Bergh Reaction.—One hundred patients were studied by weekly determinations of the icterus index and qualitative van den Bergh reaction. All icterus index determinations were made by the Bernheim method,[8] and the Gibson and Goodrich[9] modification of the van den Bergh method was used in this study. Table 4 illustrates these data.

The initial icterus index was made the day following the patient's admission to the hospital, which averaged eight and one-half days after the onset of symptoms and three and seven-tenths days after the development of jaundice. The table illustrates the characteristic rapid rise and fall of the degree of icterus, followed by a prolonged recovery period of two to six weeks before again returning to normal. The icterus index was usually not markedly elevated but ranged from a low of 16 to the amazing high of 563. A comparison of the van den Bergh reactions reveals that throughout the course of the disease the biphasic reaction was typical, but during the first two weeks a direct van den Bergh reaction was observed in over one third of the patients. In contrast to the frequency of direct reactions during the first two weeks, an indirect reaction was obtained almost entirely during the period of convalescence.

Dark Field Examination for Leptospiras.—Because of the fact that the majority of these patients were exposed to conditions which favored the transmission of Weil's disease and had frequently had to remain for days in wet fox holes, it became necessary to rule out Leptospira icterohaemorrhagiae, Leptospira canicola and other spirochetes as the etiologic agents involved.

Eighty-four dark field examinations of the blood for these organisms were made during the first ten days of the illness in 76 patients. Forty-four dark field examinations of the urine were made for 44 patients after the tenth day of the disease. In none of these examinations were leptospiras, spirochetes or spirilla demonstrated. Blood was also cultured repeatedly in Noguchi's medium and incubated at room temperature and at 37 C. under aerobic and anaerobic conditions. No evidence of growth was observed after sixteen days of incubation. Intraperitoneal inoculation of blood from 2 patients into a guinea pig also gave negative results.

Artefact spirochete-like bodies similar to those reported by Schultz[10] were frequently observed in over 50 per cent of the dark field examinations of the blood. These were considered to be artefacts, because they exhibited no active motion, were rigid and did not form spirals and could not be grown on any available medium or by inoculation in guinea pigs. They could not be stained with polychrome methylene blue or nigrosin or by silver impregnation methods. These artefacts, which were 8 to 10 microns in length and 0.5 micron in width, are mentioned only to emphasize the difficulties encountered and a possible source of error in dark field examinations of the blood. Kuzzell,[11] studying the same epidemic, has reported somewhat similar observations.

Heterophile Agglutination Test.—Because of certain similarities of this disease to infectious mononucleosis, a heterophile agglutination test was performed on 18 patients having the highest lymphocyte count and most pronounced lymphadenopathy. All results were negative.

8. Methods for Laboratory Technicians,[4] p. 119.
9. Methods for Laboratory Technicians,[4] p. 120.
10. Schultz, E. W.: The Pseudo Spirochaetes Derived from Red Blood Cells, J. Lab. & Clin. Med. **8**: 375 (March) 1923.
11. Kuzzell, W. M.: Artifact Spirochaetes in Infectious Hepatitis, M. Bull. North African Theat. Op. **1**:24 (Feb.) 1944.

Fragility Test.—In an attempt to evaluate any hemolytic factor that might be present in this disease, we studied 66 patients by determining the fragility of the red blood cells according to the method of Sanford.[12] None of these tests revealed any increased hemolysis as compared with that of the control. In fact, a majority of the tests revealed an increased resistance of the red blood cells to the hypotonic saline solution.

Sedimentation Rate.—One hundred and fifty-seven patients were studied by means of determination of the sedimentation rate according to the method of Wintrobe and Landsberg[3] with correction for anemia. These tests were performed at varying intervals throughout the course of the disease. In this group the sedimentation rate was almost invariably elevated after the first week of the disease and frequently remained persistently elevated throughout the course of the illness. Not infrequently it remained sharply elevated (25 to 30 mm.) for several weeks after the icterus index had returned to normal, slowly returning to a normal level as the hepatitis subsided or healed. The persistently elevated sedimentation rate after the icterus index had returned to normal was also compared with the clinical evidence of an active hepatitis and with evidence of hepatic dysfunction as determined by the synthesis of hippuric acid. These studies indicate that in many of these patients there was some residual activity of the hepatitis and considerable functional impairment of the liver long after the icterus index had returned to normal. In an occasional patient with mild disease there was no increase in the sedimentation rate.

Hippuric Acid Test.—One hundred and forty-three hippuric acid tests of hepatic function were performed on 88 unselected patients with infectious hepatitis at varying stages of the disease. An analysis of these results reveals that there is frequently considerable impairment of hepatic function, as determined by this test. In 21 cases the excretion of hippuric acid was repeatedly determined throughout the course of the disease and for several weeks or months after the icterus had subsided. These data are summarized in table 5.

Only 5 of the 21 patients studied by the hippuric acid test were able, after the administration of sodium benzoate, to excrete 3 Gm. or more of benzoic acid in the form of hippuric acid during the period of observation, while the remaining 15 patients were never able adequately to conjugate

12. Todd, J. C., and Sanford, A. N.: Clinical Diagnosis by Laboratory Methods, ed. 10, Philadelphia, W. B. Saunders Company, 1943, p. 327.

TABLE 5.—*Serial Studies Comparing the Results of the Hippuric Acid Test of Liver Function with the Icterus Index, the Sedimentation Rate and the White Blood Cell Count in Twenty-One Patients with Epidemic Hepatitis*

Case	Day of Illness	Icterus Index at Time of Test	Hippuric Acid, Gm.	Day Icterus Index Returned to Normal	Highest Icterus Index	Corrected Sedimentation Rate (Wintrobe)	White Blood Cells
1	16	36	....	33	48	28	4,200
	25	17	....	..	..	16	7,600
	35	10	2.72	..	..	18	6,750
	49	10	2.92	..	..	12	6,200
	61	..	4.01	..	..	..	.....
2	50	10	....	41	51	21	7,800
	60	13	....	..	..	20	8,200
	75	10	2.12	..	..	13	6,900
	87	10	1.66	..	..	..	.....
	97	8	2.26	..	..	..	.....
3	52	..	2.28	64	27	10	9,200
	65	12	2.96	..	..	3	7,400
4	132	9	2.04	132	250	40	.....
	152	8	2.76	..	..	16	9,900
	159	1	2.53	..	..	..	.....
5	110	39	1.16	135	126	36	8,900
	135	10	1.92	..	..	14	7,900
6	21	48	....	78	78	..	.....
	61	13	2.04	..	..	34	6,850
	71	15	1.88	..	..	37	.....
	83	9	2.88	..	..	21	5,800
	93	..	....	..	..	..	.....
7	18	27	....	34	27	..	7,050
	58	12	2.15	..	..	16	3,250
	68	13	1.84	..	..	5	4,350
	82	10	2.72	..	..	..	5,300
8	11	39	3.32	19	39	..	.....
	28	7	3.12	..	..	..	13,700
9	67	6	1.40	31	39	20	6,750
	80	8	1.80	..	..	32	7,000
	85	8	3.04	..	..	..	.....
10	53	14	2.72	40	150	14	5,700
	68	7	2.98	..	..	7	.....
11	36	10	....	33	32	0	6,150
	56	11	1.96	..	..	15	6,650
	68	10	2.64	..	..	4	.....
	75	10	2.36	..	..	..	.....
	85	8	2.84	..	..	..	.....
	95	10	2.72	..	..	..	.....
12	51	8	1.88	31	23	0	7,800
	73	10	2.44	..	..	..	.....
	83	9	2.80	..	..	..	.....
13	150	35	0.95	198	108	30	9,400
	177	26	1.84	..	..	30	15,700
	198	12	2.44	..	..	13	11,500
	215	10	2.48	..	..	16	10,600
	220	..	2.88	..	..	..	.....
14	42	11	2.56	42	46	12	10,700
	55	10	2.60	..	..	14	6,450
	59	10	2.92	..	..	..	.....
15	65	6	1.48	47	42	..	8,400
16	77	9	2.40	42	84	23	.....
	87	8	2.84	..	..	..	.....
17	40	114	0.00	Never normal	173	21	.....
	55	126	0.00	..	..	21	4,500
	70	126	1.28	..	..	32	6,650
18	31	22	1.52	60	111	54	9,950
	56	12	1.60	..	..	30	7,800
	69	8	1.68	..	..	21	.....
	78	6	2.04	..	..	8	7,300
	85	..	3.13	..	..	..	.....
19	51	10	2.34	30	64	15	6,900
	63	8	0.86	..	..	..	.....
	76	10	1.48	..	..	..	.....
	87	6	2.37	..	..	..	.....
20	39	12	1.69	39	84	20	5,050
	51	12	1.52	..	..	6	.....
	59	10	2.04	..	..	6	.....
	71	..	1.66	..	..	..	.....
21	14	9	1.24	14	19	10	5,500
	27	9	1.96	..	..	11	.....
	42	11	3.46	..	..	..	.....

the benzoic acid and amino acetic acid during this period. The average period required for these patients to approach a normal excretion of hippuric acid was thirty-eight days after the icterus index had returned to a normal level of 10 to 12. The actual range of time required for the functional capacity of the liver to return to a near normal after the jaundice had subsided was from one to sixty-four days and in some cases might be much longer. The exact time required for the liver to regain its normal functional efficiency is unknown, as it was not possible to follow these patients for a longer period. This evidence indicates that at least some functional impairment of the liver exists long after the icterus has subsided and the patient has seemingly recovered and is of importance in explaining why these patients so frequently had relapses after the hepatitis was apparently cured.

Unfortunately, facilities were not available at the time of this study to permit other tests of hepatic function to be performed.

Urine.—In this series of 448 patients a transitory albuminuria was noted in only 18. This always occurred during the first two weeks of the disease and was seen only in the initial urinalysis following admission in 16 of the 18 patients. In these 16 patients the albuminuria did not persist over two days. One patient had a mild albuminuria (1 to 2 plus) for seven days, and the patient who died had a persistent albuminuria until his death on the sixth day after his admission. With this exception, the albuminuria was never severe and disappeared with rest in bed and adequate fluids.

No red blood cells, white blood cells or casts were found in the urine of any of these patients, and their ability to concentrate urine was unaffected.

In contrast to the experience reported by Turner and others [13] with postvaccinal hepatitis, a high or normal specific gravity of the urine was noted in all of our patients having a transitory albuminuria. Determinations of the nonprotein nitrogen content of the blood were made on all patients having albuminuria, and in only the patient who died was this found elevated.

Stools.—The stools were carefully observed for color and bile at weekly intervals for 101 patients and less frequently for the remainder of the group. Acholic, clay-colored stools were rarely encountered, although some diminution of bile pigment was common in the stools of the majority of the patients at some time during the course of the disease.

Serologic Reactions.—The Kahn reaction of the blood was determined on 146 patients on their admission to the hospital and was negative in all except 3. The reactions of these 3 patients remained positive during only the first three weeks of the disease and subsequently became negative after the icterus subsided. These were considered false positive reactions, because there was no history or evidence of syphilitic infection in any of these patients.

Coagulation Time.—A small group of patients were studied by means of the test for coagulation time during the first five weeks of the disease. The capillary tube method [4] was used. Fifty-two tests were made at the time of the patients' admission. None of these tests revealed an abnormal coagulation time, the average coagulation time being five and nine-tenths minutes. Forty-two tests were made one week later, five of which showed a prolonged coagulation time of over eight minutes, the average time being six and one-tenth minutes. Twenty-seven tests were done during the third week, with five showing a prolonged coagulation time and with an average time of six and two-tenths minutes. During the fourth week eight tests were made, and three of these revealed evidence of a prolonged coagulation time, the average time being six and two-tenths minutes. Although the number of tests performed is small, there seemed to be an increasing tendency toward the development of a prolonged coagulation time in a small percentage of the patients studied.

Prothrombin times were not determined, as facilities for this determination were not available at the time of this study.

The relative infrequency of a hemorrhagic tendency as noted clinically was remarkable in this series. Only an occasional patient had a mild epistaxis, and in only 2 was the bleeding sufficiently prolonged to warrant the administration of vitamin K. In these 2 administration of vitamin K seemed to be effective in controlling the hemorrhage when other remedies had failed, but administration of vitamin K was ineffective in the fatal case.

The case history of the 1 fatality in the icteric group follows:

REPORT OF A CASE

A 26 year old white officer was admitted to the hospital on Dec. 23, 1943, with a chief complaint of jaundice.

13. Turner, R. H.; Snavely, J. R.; Grossman, E. B.; Buchanan, R. N., and Foster, S. D.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine, with Especial Consideration of Severe Attacks, Ann. Int. Med. **20**: 193 (Feb.) 1944.

The patient was in good health until about seven days prior to his admission, when, on December 16, he began having chills and fever associated with severe headache, backache and anorexia. He was nauseated frequently but did not vomit. These symptoms persisted, and very little fluid or food was taken. Weakness became noticeable. Four days before his admission he noted that his urine was a dark yellow, and the next day jaundice of the skin and scleras was observed for the first time. On December 21 he was admitted to an evacuation hospital, where he remained for two days. His temperature while he was there varied from 102 to 103 F. The jaundice became progressively deeper; the nausea persisted, and little or no fluid was taken. Malaise, anorexia and nausea continued, and the weakness became more pronounced.

For two months prior to the onset of this illness the patient had a diarrhea consisting of six to eight watery stools a day without pus, blood or mucus. As he felt well in all other respects, this was considered a nuisance only, and medical aid was not sought. At the onset of the illness which brought him to the hospital the diarrhea ceased. There was no previous history of jaundice or of disease of the gallbladder.

Physical examination showed a well developed and fairly well nourished man, who was extremely jaundiced and who appeared to be acutely ill. There was evidence of extreme weakness in every effort made by the patient. There were a few petechiae scattered over the abdomen and the lower part of the back. There was evidence of moderate dehydration. The cervical and axillary lymph nodes were moderately enlarged, soft and nontender. The heart was normal in size, but the sounds were of poor quality. The lungs were clear. The abdomen was soft and flat, with slight tenderness in the right upper quadrant. The liver, spleen and gallbladder were not palpable. The liver seemed small on percussion.

The blood pressure was 100 systolic and 70 diastolic. The temperature was 99 F., the pulse rate 80 and the respiratory rate 20.

Examination of the blood showed a red cell count of 3,140,000, with a hemoglobin content of 75 per cent (Tallqvist). The white blood cell count was 10,250, with 73 per cent neutrophils, 26 per cent lymphocytes and 1 per cent basophils. The urine, which was not obtained until after fluids were given, was a dark amber color with a specific gravity of 1.009. There was no albumin or formed elements, but the test for bile elicited a positive reaction. Culture of the blood, including culture for leptospiras and spirochetes on Noguchi's medium, showed no growth. A guinea pig was inoculated with the patient's blood, and two dark field examinations of the patient's serum for leptospiras were made. Results of all of these procedures were negative. The icterus index on the patient's admission was 405, and the van den Bergh reaction was direct. The quantitative van den Bergh test showed 1.74 mg. of bilirubin. Culture of the stools and examination revealed no ova or parasites. The bleeding time was five minutes. A fragility test showed beginning hemolysis in 0.34 per cent sodium chloride solution and complete hemolysis in 0.28 per cent. This result was normal as compared with the control.

A roentgenogram of the chest, made with a portable apparatus four days after his admission, showed passive congestion in the pulmonary fields. The cardiac outline appeared slightly enlarged. The patient was given a high carbohydrate liquid diet, which he tolerated well. This was supplemented daily by 1,000 cc. of an intravenously injected 5 per cent dextrose solution, keeping his daily fluid intake above 3,000 cc. After hydration was accomplished, a repeated examination of the blood two days after his admission revealed a red cell count of 1,950,000 and a white cell count of 38,600, with 82 per cent neutrophils and 18 per cent lymphocytes. Daily transfusions of 500 cc. of whole blood were given. During the first three days the patient seemed slightly improved, in spite of the fact that the watery diarrhea had returned. There was still extreme weakness, with headache and backache but with less nausea and vomiting. The icterus of the skin and scleras became deeper, and on December 28 the icterus index was 526. The liver became palpable at the right costal margin. The diet was supplemented daily by 6 multivitamin capsules,[14] 50 mg. of thiamine hydrochloride injected intravenously and 3.5 mg. of menadione in oil (vitamin K) injected subcutaneously.

On the fourth day in the hospital he began having some abdominal distention, which gradually became more pronounced. There was also generalized abdominal tenderness, but no ascites was detected. The edge of the liver was palpable 1 fingerbreadth below the costal margin and was tender. The temperature, which had ranged from 99 to 100 F. since his admission, rose to 101.8 F. The patient's condition became progressively worse. He was nauseated and retched often but did not vomit. A Levine tube was inserted into the stomach, and 1,000 cc. of dark bloody fluid was removed. The distention was controlled somewhat, but after voiding on December 28 he did not void again for thirty hours. This last specimen was of a dark green color, gave a 2 plus reaction for albumin and was strongly positive for bile. Neither tyrosine nor leucine crystals were found. An icteric frost was observed on the forehead and cheeks. The nonprotein nitrogen content was 198 mg. per hundred cubic centimeters and the icterus index 563. In spite of his steadily declining condition, the patient remained conscious. Dulness was noted at the bases of the lungs, and a few rhonchi were heard. The anemia persisted in spite of daily transfusions of whole blood. A final examination of the blood on December 29 revealed a red cell count of 2,250,000 and a white cell count of 34,300, with 95 per cent neutropils and 4 per cent lymphocytes.

The patient died on the sixth day in the hospital and the thirteenth day of his illness.

PATHOLOGIC DATA

The body was that of a well developed but poorly nourished, 26 year old white man that came to autopsy two hours post mortem.[15] The skin was intensely icteric. The main pathologic changes were confined to the kidneys, the stomach and the liver.

The left kidney weighed 310 Gm., and the right kidney weighed 280 Gm. The kidneys were dark green. The cortex measured 0.8 cm. in width. The most remarkable feature was the abnormal color. The cortical and medullary portions were deep red, in contrast to the prominent red striations. The stomach contained approximately 200 cc. of unclotted blood. The mucosa of the stomach was extremely hemorrhagic. The remainder of the gastrointestinal tract was essentially normal, except for congestion. The liver weighed 2,100 Gm. The enlargement was confined primarily to the right lobe. The liver was deep reddish brown in

14. According to the label of the package each capsule contained 2,500 U.S.P. units of vitamin A, 200 U.S.P. units of vitamin D, 1.0 mg. of thiamin hydrochloride, 1.5 mg. of riboflavin, 37.5 mg. of ascorbic acid and 10.0 mg. of nicotinamide.

15. Major David K. Gotwald, Medical Corps, Army of the United States, Chief of the laboratory service, performed the autopsy and furnished the autopsy report.

color and of a normal consistency. On section the liver appeared free of macroscopic areas of necrosis and hemorrhage. No intrahepatic or extrahepatic biliary obstruction was present. Except for a moderate enlargement of the spleen, the lymphoid elements were not remarkable.

Microscopic Studies.—The kidneys revealed an intense bile nephrosis. There were swelling and necrosis of the convoluted tubular cells. Great numbers of dense pigmented casts were present in the lower segments of the nephrons. These casts gave a staining reaction for bilirubin. The stomach showed the presence of a severe hemorrhagic gastritis. There were a moderately severe periportal inflammatory infiltration and a few minute areas of necrosis in the liver. There was no central necrosis of the lobules.

Death in this case was considered to be due to uremia resulting from the bile nephrosis occurring in the preatrophic stage of epidemic hepatitis. Weil's disease was ruled out by the absence of spirochetes in the blood and the urine on dark field examination, on guinea pig inoculation, on culture and in tissues stained for spirochetes. Yellow fever was believed to be ruled out on morphologic grounds and on the absence of exposure.

HEPATITIS WITHOUT JAUNDICE

Seventeen patients with hepatitis without jaundice were observed, and undoubtedly the diagnosis was frequently missed during the early part of this study. The following are the criteria we believe to be the most useful in establishing the diagnosis.

The history is of paramount importance and is no different from that of the usual patient with jaundice, except that fever may be negligible or the temperature may be so low that it is unnoticed and clinical jaundice never develops.

Anorexia is an early and constant symptom, with or without nausea or vomiting.

Vague gastrointestinal symptoms, gaseous eructation, ill defined abdominal discomfort or actual pain in the upper part of the abdomen or in the back behind the liver are the rule.

Easy fatigability and lassitude are common complaints. The history is frequently so vague that it is suggestive of a mild anxiety state with gastric fixation of the neurosis, and this possibility must be carefully evaluated.

On physical examination the scleras may be clear or have a faint, muddy, subicteric tint with some conjunctival injection. This tint is usually so slight that it may be easily overlooked.

The liver is usually enlarged and tender, or tenderness only is noted. The spleen is frequently enlarged.

Lymphadenopathy, especially soft enlarged axillary nodes, is a helpful finding in most of these cases. Generalized lymphadenopathy has been noted in a few cases.

Laboratory studies reveal a normal icterus index and van den Bergh reaction. Occasionally an indirect van den Bergh reaction is noted. The white blood cell count is either normal or moderately elevated, to around 12,000. A relative lymphocytosis is the rule.

Urinalysis reveals an increase in urobilinogen or a trace of bile early in the disease, but these usually disappear quickly with rest in bed and adequate fluids.

In addition to these laboratory aids, we have found that a roentgenogram of the liver and spleen may aid in determining the presence of hepatic or splenic enlargement that could not be palpated on physical examination.

Hippuric acid tests were made on 7 of the patients with hepatitis without icterus. These frequently indicated extensive functional impairment of the liver (1 to 1.5 Gm. excretion) but usually only a moderate or slight functional inefficiency was noted. For an occasional patient the excretion of hippuric acid was entirely normal.

It is our feeling that a combination of the characteristic history and the characteristic physical features, when associated with these laboratory changes, is sufficient to provide the diagnosis of this syndrome.

The diagnosis is not difficult during an epidemic, when one sees all variations of the same disease from the very mild to the most severe. It should not be difficult to make the diagnosis if one is aware of the fact that such an entity does exist. The clinical course is usually mild, and all symptoms tend to subside rapidly with rest in bed. The average duration of the illness in this group was three weeks, but it may be prolonged by inadequate rest or by excessive physical exertion prior to complete healing of the hepatitis.

The following case histories are presented to illustrate the characteristic findings in this syndrome:

REPORT OF CASES

CASE 1.—A 22 year old white man was admitted to the hospital on May 8, 1944, with the following history:

He felt well until ten days prior to his admission, when he first noted a temperature of 99.6 F. and frequent chilly sensations. The chilly sensations and low grade fever persisted for three days. Simultaneously pronounced anorexia, nausea and occasional vomiting developed, and his urine became darker, but it was clearing at the time of admission. During this period he was seen frequently by his medical officer, and two blood smears were negative for malaria parasites. No jaundice was noted. He continued to perform his duties, but extreme weakness and fatigability necessitated his admission to the hospital.

There was no history of malaria or any past history of a similar illness. Review by systems showed no abnormality.

Examination revealed a well developed and well nourished white man, who did not appear acutely ill. The physical examination revealed normal conditions except for an enlarged tender liver, which extended

3 fingerbreadths below the right costal margin. The liver was smooth and firm, without nodules, and was rather tender. There was no icterus of the scleras or skin. The spleen was not felt, and there was no lymphadenopathy. The temparature, pulse and respirations were normal.

Laboratory studies on his admission revealed an icterus index of 7. The van den Bergh reaction was negative. The red blood cell count was 4,500,000, hemoglobin content 90 per cent and white blood cell count 4,950, with 45 per cent neutrophils, 51 per cent lymphocytes, 4 per cent basophils and 1 per cent monocytes. The urine gave a negative reaction for bile but gave a positive reaction for urobilinogen in a dilution of 1 to 40. A hippuric acid test of hepatic function on the eleventh day of his illness revealed a synthesis of 2.80 Gm. The Kahn reaction of the blood was negative.

Course.—During the first week of hospitalization the patient improved rapidly and had no further nausea or vomiting. Anorexia ceased after ten days, and the liver was not palpable after the first week. No icterus developed clinically, and the icterus index on May 23 was 7, with a negative van den Bergh reaction. Urobilinogen was present in the urine in a 1:10 dilution on the nineteenth day in the hospital. Roentgenograms of the gallbladder were made and disclosed a normal functioning gallbladder without stones. The course was uneventful, and the patient was returned to duty on the twenty-first day of hospitalization. He was asymptomatic at this time, and jaundice had not been noted clinically.

Case 2.—A 19 year old white youth was admitted to the hospital on February 1 with the following history: He felt entirely well until two weeks prior to his admission, when diarrhea developed; there were five or six loose stools daily for three days. No blood, pus or mucus was noted. The diarrhea ceased, but from the onset the patient had noted severe anorexia and occasional bouts of nausea without vomiting. The anorexia became more severe; a "full" feeling in the upper part of his abdomen developed, but he had no abdominal pain.

He continued duty but felt weak and drowsy and noted that he tired easily. During this period his urine was intermittently dark-colored, but at no time was jaundice noted. Gaseous eructations and an inability to eat fatty or greasy foods developed. He had no fever, chills or other symptoms. There was no history of malaria or of disease of the gallbladder, and a careful review by systems revealed no other symptoms.

On physical examination there were seen a faint subicteric tint to the scleras and moderate enlargement of the cervical, axillary and inguinal lymph nodes. The liver was 1 fingerbreadth below the right costal margin and was tender. The spleen was not felt. The remainder of the examination revealed nothing abnormal. There was no icterus of the skin. The temperature, pulse and respirations were normal.

Laboratory studies made on his admission showed a red blood cell count of 4,460,000, a hemoglobin content of 85 per cent and a white blood cell count of 13,150, with 36 per cent neutrophils, 56 per cent lymphocytes, 7 per cent eosinophils and 1 per cent basophils. The specific gravity of the urine was 1.025, and the urine showed no sugar or formed elements but was positive for urobilinogen in a 1 to 100 dilution. The icterus index was 6; the van den Bergh reaction was negative. Examination of a thick drop for malaria gave negative results. The Kahn reaction of the blood was negative.

One week after his admission the white blood cell count was 12,800, with neutrophils 46 per cent, lymphocytes 44 per cent, monocytes 4 per cent, eosinophils 4 per cent and basophils 2 per cent. The icterus index was 8, and there was a negative van den Bergh reaction.

A roentgenogram of the liver and spleen revealed both hepatic and splenic enlargement. Roentgenologic studies of the gallbladder and stomach showed both to be normal.

Repeated examinations of the stools for parasites and ova gave negative results. Two cultures of the stools showed no typhoid-dysentery organisms.

Eleven days later the icterus index was 7 and the van den Bergh reaction negative. The white blood cell count was 8,600, with 50 per cent lymphocytes. The urine showed a trace of bile, and the reaction for urobilinogen was positive in a 1 to 20 dilution. Two heterophile agglutination tests gave negative results. A hippuric acid test of hepatic function revealed a synthesis of 2.15 Gm. in four hours. The icterus index and van den Bergh reaction remained normal. Within ten days after his admission the liver had returned to a normal size and could not be palpated.

Course.—During the first two weeks of the patient's hospitalization anorexia was severe and then gradually decreased until he became asymptomatic four weeks after his admission. At no time did clinical jaundice develop, and he was asymptomatic when discharged, on March 13.

TREATMENT

The general principles of treatment in this series were primarily concerned with relieving the patients' symptoms and preventing relapses or residual hepatic impairment.

A high carbohydrate, low fat, moderate protein diet was the standard type used and was tolerated well. Multivitamin tablets [14] were given to all patients throughout the course of the illness as a supplement to the low fat diet.

In addition to these measures, intermediate feedings of fruit juices and hard candy were given to all the patients between meals. This supplemented the caloric intake and seemed to be of value during the early part of the illness, when the intake of food was at its lowest level.

Rest in bed, especially during the early stages of the disease, is considered to be more essential in promoting a rapid recovery and in preventing relapses than any other single factor.

If sufficient rest is obtained, relapses can be reduced to a minimum and the tendency for a chronic hepatitis to develop can be avoided in the vast majority of these cases. If a relapse develops, further rest in bed and avoidance of physical fatigue promptly relieve the patient's symptoms.

Of importance almost equal to rest in bed is an adequate intake of fluids. These can be in the form of water or fruit juices, the latter being especially efficacious and well tolerated. A fluid intake of at least 3,000 cc. daily is considered essential for the prompt relief of the patient's symptoms and of the degree of icterus. At no time should the patient be allowed to become dehydrated.

An example of the serious consequences of an inadequate fluid intake is shown in the single fatality in this series. The patient had been able to obtain only a meager supply of water during the week preceding his hospitalization and had a severe diarrhea which further dehydrated him. As a result, a severe bile nephrosis developed, producing irreversible changes in the renal tubules, which undoubtedly contributed to his death.

Since relapses frequently developed in patients who had an intercurrent infection of the respiratory tract, care should be taken to shield the patient from respiratory infections of any type.

COMMENT

A comparison of the clinical observations on patients with epidemic hepatitis with those of patients with postvaccinal hepatitis reveals several differences worthy of mention.

Of the patients with postvaccinal hepatitis, as reported by Turner and his co-workers,[18] only an occasional one had fever, whereas fever, chills and evidence of an infectious process was an outstanding feature in 61 per cent of the patients in this group. The incidence of various types of dermatitis in the patients with postvaccinal type of hepatitis was much more frequent than in those with epidemic hepatitis. Only 2 per cent of our patients exhibited any type of dermatitis, in contrast to the high incidence of dermatitis in the postvaccinal group. Lymphadenopathy, frequently pronounced in this series, is not mentioned in the reports on cases of postvaccinal hepatitis. There seemed to be a more frequent tendency for anemia and severe complications to develop in the latter group. Psychic reactions were not observed in any of our patients. It is noteworthy that even in the rapidly fatal case in this series the patient's mental reaction remained clear until he died.

When epidemic hepatitis is compared with catarrhal jaundice, it is apparent that the observations are quite similar. We do not feel that we can distinguish any significant differences between acute infectious (epidemic) hepatitis and catarrhal jaundice. The term "acute infectious" (or "epidemic") hepatitis seems to be preferable to the term "catarrhal jaundice," for describing this disease. The latter term is misleading, as there is definite evidence of hepatic parenchymal and hepatocellular involvement and as hepatitis without jaundice is relatively common.

There is no doubt in our minds that this is frequently a serious disease, which by its seemingly benign course may mislead both the patient and the clinician. A prolonged convalescent period is required before hepatic functional efficiency is restored to normal and the patient is to be considered well.

SUMMARY AND CONCLUSIONS

Two hundred and thirty-eight patients with epidemic hepatitis with jaundice and 17 patients with hepatitis without jaundice were studied by various clinical and laboratory methods during the six month period from Nov. 16, 1943 to May 16, 1944. A total of 448 patients with hepatitis with jaundice were observed during this period. There was 1 death in this series.

The clinical characteristics of hepatitis without jaundice were studied.

The clinical characteristics of epidemic hepatitis with jaundice were found to be not essentially different from those of catarrhal jaundice.

Clinically, epidemic hepatitis is similar to postvaccinal hepatitis but differs in the frequent occurrence of chills, fever and lymphadenopathy and in the relative absence of dermatitis, anemia and mental reactions.

Fever, chills and other evidence of an acute infectious, systemic disease are common initial symptoms.

The disease is usually mild but has a frequent tendency to relapse with exertion, excessive physical fatigue and intercurrent infections. Relapses can be prevented or minimized by adequate rest in bed and by a prolonged convalescent period.

The disease, although usually benign, may be rapidly fatal. Repeated severe hemorrhages from ulcerations in the gastrointestinal tract and nephrosis due to depositions of bile pigment in the renal tubules were noteworthy complications in the fatal case.

The icterus index, although useful in following the course of the disease, is not a reliable guide in determining either the activity of the hepatitis or the degree of hepatic functional impairment following an attack of epidemic hepatitis. The degree of icterus does not always indicate the severity of hepatic damage.

The hippuric acid test of hepatic function frequently indicates residual hepatic functional impairment long after the icterus index has returned to normal.

The sedimentation rate is useful in determining the residual activity of the hepatitis and frequently remains elevated for several weeks after the icterus index has returned to normal.

A prolonged convalescence and conservative management of the patients are important in treatment.

Progress in Internal Medicine

INFECTIOUS DISEASES

ELEVENTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

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In the preparation of these reviews, during each succeeding year of the war, I have expected my task to be easier because of apparent distractions in investigative work. Instead, there has been an ever increasing amount of important contributions to the knowledge of infections to review. First came studies of many sulfonamide compounds, their modes of administration, their pharmacology and their effect on many infections; then followed the introduction of penicillin, its route of administration, its pharmacology and its effect on various diseases, and now such studies are being made on substances which attack gram-negative bacilli. So rapidly have advances been made that for certain diseases sulfonamide therapy is already regarded as old fashioned and serum therapy is only rarely used. The full import of all these discoveries during the turmoil of war will be even more fully appreciated later. This era is as important as the Pasteur-Koch epoch in the field of infectious diseases.

Advances in knowledge of exotic diseases like malaria, filariasis and typhus have gone apace with the worldwide dispersal of military personnel. Evidence is accumulating that filtrable viruses cause many more diseases than were known of before. Numerous "new" viral infections of the central nervous system and of the respiratory tract are established as entities. Infectious hepatitis is shown to be almost certainly of viral origin, and evidence points to viruses as causes of infections of the gastrointestinal tract and urinary tract, areas heretofore unassociated primarily with viral diseases. At the same time advances were made in the study and control of air-borne infection.

PENICILLIN

In the month of April 150 billion units of penicillin was allocated for civilian use; in June a total of 650 billion units was made, and for August 800 billion is in prospect. The tremendous decrease of the cost to about 49 cents per 100,000 units makes it doubtful if synthesis on a commercial scale will be attempted. Penicillin will soon be available in tablet and in liquid form for oral administration.

In addition to the great benefits derived therefrom, there is reason to fear [1] that the release of penicillin will be followed by the same abuse, waste and commercialization that followed the release of the sulfonamide compounds. It is perhaps too much to hope that all physicians, druggists, laymen in general and the drug industry will cooperate in the proper use of penicillin. Regulation by some official body may be needed to prevent absurd combinations of penicillin with chewing gum, mouth wash, cough drops, skin lotions and so forth. The use of penicillin pastilles [2] has already been recommended for Vincent's stomatitis and even for diphtheria, for either of which the value of penicillin is doubtful. It has already been suggested, facetiously it is hoped, that a combination of a sulfonamide compound, penicillin and streptomycin will control most infections without need for further diagnoses.

Penicillin is preferable to sulfonamide compounds in the treatment of pneumococcus, hemolytic streptococcus and staphylococcus pneumonia [3] and of pneumococcus meningitis but not of meningococcus meningitis.[4] Penicillin also seems to be of more value and safer than sulfonamide compounds in the treatment of severe

From the Jefferson Medical College and Hospital.

1. Falk, L. A., and Goodman, H.: Will Penicillin Be Used Indiscriminately? Correspondence, J. A. M. A. **127**:672 (March 17) 1945.

2. MacGregor, A. B., and Long, D. A.: Use of Penicillin Pastilles in Oral Infections: Preliminary Report, Brit. M. J. **2**:686-688 (Nov. 25) 1944.

3. (*a*) Craig, W. M., and others: Penicillin: A Progress Report Based on 1,455 Cases Treated at the National Naval Medical Center, Bethesda, Maryland, U. S. Nav. M. Bull. **44**:453-479 (March) 1945. (*b*) Lueck, A. G., and Edge, C. O.: Penicillin in Pneumonia, ibid. **44**:480-485 (March) 1945.

4. Meads, M.; Harris, H. W.; Samper, B. A., and Finland, M.: Treatment of Meningococcal Meningitis with Penicillin, New England J. Med. **231**:509-517 (Oct. 12) 1944.

infections of the throat caused by hemolytic streptococci. Plummer and his colleagues [5] on several occasions noted the development of hemolytic streptococcus peritonsillar abscess, pneumonia and empyema in patients who were receiving sulfadiazine. With penicillin therapy, improvement was usually evident within eight to twelve hours after the first injection of 15,000 units, after which injections were then given every four hours. Treatment should be continued for six days lest relapse occur. Hemolytic streptococci disappeared promptly from the nasopharynx but often reappeared after treatment was stopped. These authors recommend the injection of penicillin without delay in case of any serious, progressive hemolytic streptococcus infection but not for mild sore throat. Since mild pharyngitis occurs during many other infectious diseases not associated with the hemolytic streptococcus, much penicillin will be wasted unless cultures are made in each instance before therapy. No one by inspection alone can make an accurate diagnosis of a "strep throat." Group D hemolytic streptococci are much more resistant to the action of penicillin than those of other groups.[6]

Further experience leads Spink,[7] who once strongly favored the use of sulfonamide compounds for staphylococcic infections, to write that penicillin is the more effective therapeutic agent. The same conclusion concerning the use of penicillin applies to certain infections caused by hemolytic streptococci. Evidence of the development of resistance of staphylococci to penicillin appeared in his studies.

The value of penicillin in surgery is discussed in the July 1944 issue of the *British Journal of Surgery*. According to Meleney,[8] penicillin may be expected to give good results in 75 per cent of cases of grave infection by hemolytic streptococci but less often when mixed infection is present.

For Subacute Bacterial Endocarditis.—Reports of an exhaustive study of subacute bacterial endocarditis by Kelson and White appears in the January 1945 issue of the *Annals of Internal Medicine*. Studies were made before and after the advent of sulfonamide drugs and penicillin. Before 1939 no treatment was effective, and all of 245 patients studied died from the disease; the patient surviving longest lived nineteen months after the onset. After sulfonamide therapy was introduced, 7 (19 per cent) of 79 patients recovered. Seventeen of the treated patients received heparin in addition; 3 of these recovered. Of 9 patients given large doses of penicillin, 6 (67 per cent) have shown "a definite control (perhaps a cure)," but up to the time of publication of the report only eight months had elapsed. Further study is necessary. Dawson and Hunter [9] also report promising results in the treatment of 27 patients, of whom 21 were greatly benefited, for a period of many months. These and other authors, including me, are not sure that heparin is needed as an adjuvant in the treatment. The arbitrary dosage of penicillin they recommend is 200,000 units daily for three weeks. Larger or smaller amounts may be needed. The intramuscular drip method of administration is recommended. Paullin and McLaughlin [10] report 3 "cures" among 6 patients and others [11] 7 among 9 patients. According to Loewe,[12] if the patient is in good physical condition, the duration of the disease less than three months and the causative organism sensitive to penicillin a satisfactory result may be expected, barring accidents, "in virtually every case." While this statement may be true, it must be remembered that the injured valve remains even after "cure" and the ubiquitous Streptococcus viridans is ready for reinvasion when opportunity is favorable.

An interesting but little emphasized sidelight emerged from one study, namely, that dental extraction was second only to infections of the upper respiratory tract as an inciting cause of the disease. A history of recent dental operations was given in 25 per cent of cases.

In an editorial comment [13] on some of these studies it is stated that it is not yet possible to

5. Plummer, N. A., and others: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, J. A. M. A. **127**:369-374 (Feb. 17) 1945.

6. Watson, R. F.: Sensitivity of Various Serological (Lancefield) Groups of Streptococci to Penicillin, Proc. Soc. Exper. Biol. & Med. **57**:65-69 (Oct.) 1944.

7. Spink, W. W., and Hall, W. H.: Penicillin Therapy at the University of Minnesota Hospitals: 1942-1944, Ann. Int. Med. **22**:511-525 (April) 1945. Spink, W. W.; Hall, W. H., and Ferris, V.: Clinical Significance of Staphylococci with Natural or Acquired Resistance to Sulfonamides and to Penicillin, J. A. M. A. **128**:555-559 (June 23) 1945.

8. Meleney, F. L.: Recent Experiences with Penicillin in the Treatment of Surgical Infections, Bull. New York Acad. Med. **20**:517-537 (Oct.) 1944.

9. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. A. M. A. **127**:129-137 (Jan. 20) 1944.

10. Paullin, J. E., and McLaughlin, C. J.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, Ann. Int. Med. **22**:475-484 (April) 1945.

11. Meads, M.; Harris, H. W., and Finland, M.: The Treatment of Bacterial Endocarditis with Penicillin, New England J. Med. **232**:463-474 (April 20) 1945.

12. Loewe, L.: The Combined Use of Anti-Infectious and Anticoagulant Agents in the Treatment of Subacute Bacterial Endocarditis, Bull. New York Acad. Med. **21**:59-86 (Feb.) 1945.

13. Treatment of Subacute Bacterial Endocarditis, editorial, Ann. Int. Med. **27**:131-133 (Jan.) 1945.

reach a definite conclusion as to the efficacy of the measures tested or whether heparin is of added value or not. The procedures are still in the experimental stage. Nevertheless, penicillin is by far the most effective agent ever used for the treatment of subacute bacterial endocarditis.

For Various Other Diseases.—Penicillin was of value in the treatment of ornithosis or psittacosis,[14] yaws,[15] and rat bite (Streptobacillus moniliformis) fever.[16] Anthrax [17] was apparently controlled, although the bacillus is relatively resistant in the test tube. Penicillin caused great improvement in the pustular eruption of smallpox after sulfathiazole had failed.[18] Conflicting reports concern its value for leptospirosis; in one paper [19] no beneficial effects were noted, and in two others [20] it was reported that improvement seemed to depend on its use. Penicillin was effective in treating artificially infected guinea pigs,[21] mice and hamsters.[22] In the study on mice and hamsters, penicillin and specific immune serum seemed to have equal therapeutic values.

In treatment of experimental syphilis in rabbits, even large doses were not sufficient to kill all the spirochetes, although the primary lesions healed satisfactorily.[23] In treatment of human syphilis, British workers [24] record immediate favorable responses in all cases of early infections. If one judges by later effects, the arsenical compounds and bismuth might have given better results. The doses used were 30,000 units intramuscularly every three hours for eighty injections, or 2,400,000 units in ten days, or 30,000 units every hour for forty injections (1,200,000 units). The need for frequent injections makes routine treatment inconvenient. Excellent immediate results are reported [25] in the treatment of acute syphilitic meningitis with 600,000 to 4,000,000 units of penicillin given over a period of eight to sixteen days. It is still too early to be able to predict the later course of the infection.

Penicillin has no beneficial effect in the treatment of viral pneumonia,[38] rheumatoid arthritis,[26] tularemia,[27] leprosy,[28] tetanus [29] or of inoculation malaria.[30] Penicillin was without effect on the multiplication of the viruses of vaccinia, St. Louis encephalitis and equine encephalitis; it did inhibit the growth of the "viruses" of psittacosis and mouse meningopneumonitis in chick embryos, but such great amounts were required as to render its practical importance doubtful.[31] However, 2 recorded patients [14] and 1 of my own with psittacosis seemed to be benefited by penicillin. The clinical value of penicillin, as in the case of anthrax, cannot always be judged by its action on the experimental animal or in the test tube.

Penicillin gives little or no benefit to patients with bronchiectasis.[32] It is helpful for chronic bronchitis, often immediately so, causing a disappearance of cough and sputum. Inhaled nebu-

14. Turgasen, F. E.: Human Ornithosis Treated with Penicillin, J. A. M. A. **126**:1150-1151 (Dec. 30) 1944. Flippin, H. F.; Gaydosh, M. J., and Fittipoldi, W. V.: Penicillin for Human Psittacosis, ibid. **127**: 280-281 (May 26) 1945.

15. Whitehill, R. C., and Austrian, R.: Treatment of Primary and Secondary Yaws with Penicillin, Bull. Johns Hopkins Hosp. **75**:232-240 (Oct.) 1944.

16. Altemeier, W. A.; Snyder, H., and Howe, G.: Penicillin Therapy in Rat Bite Fever, J. A. M. A. **127**: 270-273 (Feb. 3) 1945.

17. Murphy, F. D.; LaBoccetta, A. C., and Lockwood, J. S.: Treatment of Human Anthrax with Penicillin, J. A. M. A. **126**:948-950 (Dec. 9) 1944.

18. Jeans, W. D.; Jeffrey, J. S., and Gunders, K.: Penicillin and Smallpox: Report of Four Cases, Lancet **2**:44-46 (July 8) 1944.

19. Bulmer, E.: Weil's Disease in Normandy: Its Treatment with Penicillin, Brit. M. J. **1**:113-114 (Jan. 27) 1945.

20. Hart, V. L.: A Case of Weil's Disease Treated with Penicillin, Brit. M. J. **2**:720 (Dec. 2) 1944. Cross, R. M.: Penicillin in Weil's Disease, Lancet **1**:211-212 (Feb. 17) 1945.

21. Alston, J. M., and Broom, J. C.: The Action of Penicillin on Leptospira and on Leptospiral Infections in Guinea Pigs, Brit. M. J. **2**:718-719 (Dec. 2) 1944.

22. Larson, C. L., and Griffitts, J. J.: A Comparison of the Effect of Penicillin and Immune Serum in the Treatment of Experimental Leptospirosis in Young White Mice and in Hamsters, Pub. Health Rep. **66**: 317-323 (March 23) 1945.

23. Ercoli, N., and Lafferty, L. C.: The Anti-Spirochetal Activity of Penicillin in Experimental Infections, Proc. Soc. Exper. Biol. & Med. **57**:4-6 (Oct.) 1944.

24. Ross, A. O. F., and others: Treatment of Early Syphilis with Penicillin, Lancet **2**:845-848 (Dec. 30) 1944.

25. Nelson, R. A., and Duncan, L.: Acute Syphilitic Meningitis Treated with Penicillin, Bull. Johns Hopkins Hosp. **75**:327-352 (Dec.) 1944.

26. Boland, E. W.; Headley, N. E., and Hench, P. S.: The Effect of Penicillin on Rheumatoid Arthritis, J. A. M. A. **126**:820-823 (Nov. 25) 1944.

27. Josey, A. I.: Penicillin Treatment of a Case of Tularemia Without Effect, J. A. M. A. **126**:496-497 (Oct. 21) 1944.

28. Faget, G. H., and Pogge, R. C.: Penicillin Treatment of Leprosy: Clinical Note, Pub. Health Rep. **60**: 324-325 (March 23) 1945.

29. Buxton, R., and Kurman, R. L.: Tetanus: Report of Two Cases Treated with Penicillin, J. A. M. A. **127**: 26 (Jan. 6) 1945.

30. Hindle, J. A.; Rose, A. S.; Trevett, L. D., and Prout, C.: The Effect of Penicillin on Inoculation Malaria: A Negative Report, New England J. Med. **232**:133-136 (Feb. 1) 1945.

31. Parker, R. F., and Diefendorf, H. W.: Effect of Penicillin on Certain Viruses, Proc. Soc. Exper. Biol. & Med. **57**:351-354 (Dec.) 1944.

32. Stookey, P. F., and others: Penicillin Therapy in Bronchiectasis, South. M. J. **38**:98-102 (Feb.) 1945.

lized penicillin caused improvement in 5 of 20 patients studied by others.[33] Simplified methods for the clinical measurement of penicillin in the blood and the determination of the sensitivity of bacteria to it are described.[34]

In a study of reasons for the failure of penicillin to cure certain diseases, Bloomfield and his co-workers [35] classify them as follows: (*a*) insufficient dosage, (*b*) insufficient surgical drainage, (*c*) overwhelming infection or lack of resistance even to penicillin-sensitive bacteria and (*d*) progression of other conditions (for example, nephritis); penicillin fastness is apparently of little importance.

Methods of Administration.—Oral Therapy: Penicillin may be given orally. Some of it is lost in the intestinal tract, but if the doses given are large as compared with those used for parenteral injection, satisfactory amounts may be attained in the blood. According to McDermott's [36] group, about five times as much must be given orally to obtain levels comparable to those obtained after intramuscular injection. In another study [37] it was reported that 1.5 to 7 Gm. of trisodium citrate given with penicillin two hours after breakfast greatly increases its absorption. According to György and his co-workers,[38] penicillin calcium given orally with trisodium citrate was as effective in the treatment of gonorrhea as the same dose given parenterally. Oral administration of 250,000 to 300,000 units over a period of sixteen to twenty hours gave good results. British investigators [37b] used with success the combined stabilizing effect of egg albumin and the buffer action of sodium bicarbonate, and others [39] used cottonseed oil. After a single dose of 90,000 units, the amounts in the blood reached 0.05 units in one hour and lasted four hours, which is about the level usually attained in clinical practice after the intramuscular injection of 20,000 units. Possible advantages of oral therapy are slower absorption, its longer duration in the blood and the fact that the product used need not be highly purified. A disadvantage might be the tendency to indiscriminate use and a waste of material, as with the sulfonamide compounds.

Penicillin given rectally in suppositories appears in the blood in effective amounts.[40]

Parenteral Therapy: Penicillin injected intramuscularly is demonstrable in the blood for longer periods if the vehicle is a 5 per cent solution of dextrose instead of an isotonic solution of sodium chloride.[41] Penicillin can be kept in the blood longer if epinephrine hydrochloride is injected intramuscularly with it [42] and also if a combination of penicillin with human plasma, making a penicillin-protein complex, is given intravenously.[43]

Inhalation Therapy: Barach and his aids [33] investigated the usefulness of inhaled, nebulized penicillin aerosol for the treatment of pulmonary infection. When inhaled, penicillin appears in small amounts in the blood, but the aim was not so much to obtain large amounts in the blood as large amounts locally. Perhaps combined parenteral injection and inhalation therapy is desirable for the treatment of pulmonary abscess, bronchiectasis or other bronchial infections. British observers [44] feel that inhalation therapy with penicillin has a number of advantages because it obviates oft repeated injections, especially for infants, and because penicillin is so rapidly excreted when administered otherwise.

33. Barach, A. L., and others: Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess: Preliminary Report, Ann. Int. Med. **22**:485-509 (April) 1945.

34. Cooke, J. V. A.: Simple Clinical Method for the Assay of Penicillin in Body Fluids and for Testing of Penicillin Sensitivity of Bacteria, J. A. M. A. **127**: 445-449 (Feb. 24) 1945.

35. Bloomfield, A. L.; Kirby, M. M., and Armstrong, C. D.: A Study of "Penicillin Failures," J. A. M. A. **126**:685-691 (Nov. 11) 1944.

36. McDermott, W.; Bunn, P. A.; Benoit, M.; DuBois, R., and Haynes, W.: Oral Penicillin, Science **101**:228-229 (March 2) 1945.

37. (*a*) Charney, J.; Alburn, H. E., and Bernhart, F. W.: Urinary Excretion of Penicillin in Man After Oral Administration with Gastric Antacids, Science **101**: 251-253 (March 9) 1945. (*b*) Little, C. D. H., and Lumb, G.: Penicillin by Mouth, Lancet **1**:203-206 (Feb. 17) 1945.

38. György, P., and others: Administration of Penicillin by Mouth, J. A. M. A. **127**:639-642 (March 17) 1945.

39. Libby, R. L.: Oral Administration of Penicillin in Oil, Science **101**:178-180 (Feb. 16) 1945.

40. Loewe, L., and others: Administration of Penicillin by Rectal Suppository, J. A. M. A. **128**:18 (May 5) 1945.

41. Armstrong, C. D.; Halpern, R. M., and Cutting, W. C.: Prolongation of the Action of Penicillin After Intramuscular Injection, Proc. Soc. Exper. Biol. & Med. **58**:74-76 (Jan.) 1945.

42. Fisk, R. T.; Foord, A. G., and Alles, G.: Prolongation of Penicillin Activity by Means of Adrenalin, Science **101**:124-125 (Feb. 2) 1945.

43. Chow, B. F., and McKee, C. M.: Interaction Between Crystalline Penicillin and Human Plasma Proteins, Science **101**:67-68 (Jan. 19) 1945; Inactivation of the Antibiotic Activity of Penicillin by Cysteine Hydrochloride: I. Clinical Aspects of Inactivation, Proc. Soc. Exper. Biol. & Med. **58**:175-177 (Feb.) 1945. Cavallito, C. J., and Bailey, J. H.: Preliminary Note on the Inactivation of Antibiotics, Science **100**: 390 (Oct. 27) 1944.

44. Knott, F. A., and Clark, W. H.: Absorption of Aerosol Penicillin via the Lungs, Lancet **1**:468-469 (April 14) 1945.

Bacteriologic Studies of Resistance to Penicillin.—Escherichia coli,[45] Eberthella typhosa, Bacillus proteus and Salmonella[46] are not as resistant to the effect of penicillin as was once thought. Furthermore, their susceptibility can be increased by adding methionine and normal serum to the culture medium. From cultural experiments on Esch. coli and Salmonella in synthetic medium rather than in meat infusion broth, it appeared that casein hydrolysate, asparagine, glutamic acid and other amino acids partially antagonize the effect of penicillin. The resistance of gram-negative bacilli to penicillin therefore seems at least to some extent, to be extrinsic in nature.

Different strains of staphylococci, according to Neter,[47] vary in their susceptibility to penicillin, tyrothricin and streptomycin in culture medium. Their susceptibility to the effects of one antibiotic is not always the same as that to the effects of another. If the same variation occurs in the body during infection, it would be desirable beforehand to determine and to select the most effective antibiotic agent for treatment. Staphylococci may become resistant to both sulfonamide compounds and penicillin.[7]

According to Demerec,[48] induced resistance of a strain of staphylococcus to penicillin results from the appearance of variant forms, which survive because they are resistant while the sensitive forms disappear. Resistance itself is not related to pathogenicity,[49] and the course of infection proceeds regardless of changes in resistance to penicillin. Gallardo, like Spink, found about 13 per cent of pathogenic strains of staphylococci to be naturally resistant to penicillin; another 9 per cent become resistant during treatment with penicillin. The resistance which bacteria develop against penicillin, especially if developed in vitro, may not be permanent. Two strains of staphylococci which became resistant rapidly lost this property on further subculture in broth.[50] It is probable that penicillin-sensitive variants reappear in culture mediums. Gonococci may become resistant to penicillin by growth in a medium containing it.[51] Morphologic changes as well as differences in fermentation reactions appeared in the resistant forms.

Kirby[52] shows that resistant staphylococci produce a penicillin-inactivating substance, but the staphylococci themselves are inhibited by penicillin and will not survive unless great numbers are present. In contrast with other bacteria, staphylococci are said to disintegrate when subjected to penicillin; the lysed cellular elements may be partly responsible for the fever and toxicity of infections which these bacteria cause. According to Todd,[53] however, all penicillin-sensitive micro-organisms are susceptible to bacteriolysis by penicillin.

Other Studies on Penicillin.—Penicillin is inactivated by cysteine; it also combines with human serum albumin[43] and, contrary to previous views, is inactivated in varying degrees by contact with human blood[54] when certain bacteria are used as test organisms, probably owing to the presence in the blood of penicillinase produced by penicillin-resistant bacteria. Penicillin is both bacteriostatic and bactericidal at temperatures as high as 42 C.[55] It is doubtful if it acts only on dividing cells.

The mode of action of penicillin on bacterial growth is as hard to understand as is the action of the sulfonamide compounds.[56] Penicillin is bactericidal, but even in a culture of bacteria mixed with penicillin there are almost always a few surviving or visible bacteria. This persistence is explained on the basis of the appearance and survival of penicillin-resistant variants. One theory, perhaps too simple to account for the bactericidal effect, assumes that penicillin prevents cell division but not cell growth; the cell increases in size and bursts. Lysis of bac-

45. Shwartzman, G.: (*a*) Inhibition of E. Coli by Penicillin, Science **100**:477-478 (Nov. 24) 1944; (*b*) On the Nature of Refractiveness of Certain Gram-Negative Bacilli to Penicillin, ibid. **101**:276-277 (March 16) 1945.

46. Steiner, M.: Gram-Negative Bacilli Susceptibility to Penicillin, U. S. Nav. M. Bull. **44**:486-493 (March) 1945.

47. Neter, E.: Relative Susceptibility of Staphylococci to the Bacteriostatic Action of Antibiotics, Proc. Soc. Exper. Biol. & Med. **58**:126-128 (Feb.) 1945.

48. Demerec, M.: Production of Staphylococcus Strains Resistant to Various Concentrates of Penicillin, Proc. Nat. Acad. Sc. **31**:16-20 (Jan.) 1945.

49. Gallardo, E.: Sensitivity of Bacteria from Infected Wounds to Penicillin: II. Results in 112 Cases, War Med. **7**:100-110 (Feb.) 1945.

50. Todd, E. W.; Turner, G. S., and Drew, L. G. W.: The Temporary Character of "Fastness" of Staphylococci to Penicillin, Brit. M. J. **1**:111-113 (Jan. 27) 1945.

51. Bahn, J. M.; Ackerman, H., and Carpenter, C. M.: Development in Vitro of Penicillin-Resistant Strains of Gonococcus, Proc. Soc. Exper. Biol. & Med. **58**:21-24 (Jan.) 1945.

52. Kirby, W. M. M.: Bacteriostatic and Lytic Actions of Penicillin on Sensitive and Resistant Staphylococci, J. Clin. Investigation **24**:165-169 (March) 1945.

53. Todd, E. N.: Bacteriolytic Action of Penicillin, Lancet **1**:74-77 (Jan. 20) 1945.

54. Bigger, J. W.: Inactivation of Penicillin by Serum, Lancet **2**:400-402 (Sept. 23) 1944.

55. Garrod, L. P.: Action of Penicillin on Bacteria, Brit. M. J. **1**:107-110 (Jan. 27) 1945.

56. How Penicillin Works, Lancet **1**:276-277 (March 3) 1945.

teria is commonly observed in the presence of penicillin. Perhaps penicillin kills bacteria with a minimum of disturbance to the bacterial protoplasm, so that autolysis takes place readily.

Taxonomists may be alarmed by the report of one hundred new strains, or "mutations," arising from a strain of Penicillium notatum after bombardment with neutrons.[57] The idea back of the experiment was to induce the appearance of variant forms which may be even better producers of penicillin than the parent form. The appearance of so many variant forms suggests that the phenomenon of microbic variation is far more complex than is usually believed, as indicated also by earlier studies on Micrococcus tetragenous (Gaffkya tetragena), in which more than twenty variants appeared.

STREPTOMYCIN AND OTHER ANTIBIOTICS

Although increasingly pure preparations of penicillin inhibit the growth of many gram-negative bacilli,[58] the effectiveness is not great enough to promise beneficial therapeutic results in infections they cause. Accordingly, attention is now being given to streptomycin, an extract of Actinomyces griseus, similar in many respects to streptothricin.[59] Streptomycin has the advantage of higher potency against certain pathogenic bacilli; it is not decomposed by any bacteria so far tested, and it is not toxic for the host. At present streptomycin is effective against a number of diseases caused by gram-negative bacilli in animals[60]: tularemia, tuberculosis and infections with Friedländer's bacillus (Klebsiella pneumoniae). It is of less value than penicillin for infections with Borrelia novyi and with Leptospira icterohaemorrhagiae.[61]

Thus far not enough patients with systemic infections have been treated with streptomycin to permit a judgment of its value, but the results are promising. Recovery took place during treatment of 4 of 7 patients with typhoid.[62] The fact that amounts appeared in the blood greater than those needed to kill the bacteria in culture suggests that streptomycin aided in recovery. The results obtained were less impressive than the results of penicillin therapy for certain other diseases. No explanation is available to account for the failures except that unknown factors in the body may protect the bacilli from the drug or may interfere with its action.

At a recent conference at Rahway, N. J., promising results were reported by Foshay in the treatment of tularemia; a few patients with brucellosis seemed to have been helped, but, again as in typhoid, others were not. Because streptomycin given parenterally is largely excreted in the urine, it is effective in many instances in eliminating Esch. coli, B. proteus and Bacillus pyocyaneus from the urine, but only if the bacteria present happen to be sensitive to drugs.[63] Streptomycin given orally is almost all excreted in the feces. Here, it successfully suppresses or eliminates Esch. coli and other bacteria if they are drug sensitive. When given parenterally, theoretically sufficient amounts appear in the spinal fluid, but no evidence of benefit was obtained in patients with tuberculous meningitis.[63] The effects on Hemophilus influenzae meningitis were unimpressive, as were those on pulmonary tuberculosis. Yet in experimental animals, streptomycin was of greater value than any substances yet tested for tuberculosis. Reports of the use of streptomycin in treating cholera, plague and bacillary dysentery are eagerly anticipated.

Crystalline preparations of both streptomycin and streptothricin have been made.[64]

Energetic search is under way to test the ability of many species of fungi to make antibiotic substances. Some of them already give indication of being effective against certain filtrable viruses.[65] A new substance, chaetomin, which is active principally against gram-positive bacteria,

57. Myers, W. G., and Hanson, H. J.: New Strains of Penicillium Notatum Induced by Bombardment with Neutrons, Science **101**:357-358 (April 6) 1945.

58. Hobby, G. L.: The Antibacterial Action of Penicillin Against Gram-Negative Organisms, Science **100**: 500-501 (Dec. 1) 1944. Shwartzman.[45a]

59. Waksman, S. A.; Bugie, E., and Schatz, A.: Isolation of Antibiotic Substances from Soil Microorganisms, with Special Reference to Streptomycin and Streptothricin, Proc. Staff Meet., Mayo Clin. **17**:537-548 (Nov. 15) 1944.

60. Heilman, F. R.: Streptomycin in the Treatment of Experimental Tularemia, Proc. Staff Meet., Mayo Clin. **19**:553-559 (Nov. 29) 1944. Feldman, W. H., and Hinshaw, H. C.: Effects of Streptomycin in Experimental Tuberculosis in Guinea Pigs, ibid. **19**:593-599 (Dec. 27) 1944. Heilman, F. R.: Streptomycin in the Treatment of Experimental Infection with Microorganisms of the Friedländer Group (Klebsiella), ibid. **20**:33-39 (Feb. 7) 1945.

61. Heilman, F. R.: Streptomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagiae (Weil's Disease), Proc. Staff Meet., Mayo Clin. **20**:169-176 (May 30) 1945.

62. Reimann, H. A.; Elias, W. F., and Price, A. H.: Streptomycin for Typhoid Fever: A Pharmacologic Study, J. A. M. A. **128**:175-180 (May 19) 1945.

63. Reimann, H. A.; Price, A. H., and Elias, W. F.: To be published.

64. Fried, J., and Wintersteiner, O.: Crystalline Reineckates of Streptothricin and Streptomycin, Science **101**:613-615 (June 15) 1945.

65. Jones, D.; Baudette, F. R.; Geiger, W. B., and Waksman, S. A.: A Search for Virus-Inactivating Substances Among Microorganisms, Science **101**:665-668 (June 29) 1945.

has been prepared.[66] Antibiotics derived from Aspergillus are active against the tubercle bacillus but not against staphylococci.[67] Russians isolated a substance called gramicidin S, which inhibits the growth of a variety of both gram-positive and gram-negative bacteria.[68] In one study, tyrothricin sprayed twice daily into the throats of carriers had no effect in eliminating hemolytic streptococci.[69]

The juice and steam distillate of juice of buttercups [70] is strongly antibiotic for a number of pathogenic gram-positive and gram-negative bacteria, for Mycobacterium tuberculosis and for certain yeasts. Certain chemicals, among them urethane (butyl carbamate),[71] are bacteriostatic and bactericidal for gram-negative bacteria and to some extent for gram-positive ones. They are said to be of value in the treatment of infections caused by gram-negative bacteria. Another compound, 2, 4-dichlorophenoxyacetic acid, retards certain gram-positive bacteria.[72]

Attempts at the synthesis of antibiotics are in progress, and success has been reported in the preparation of an isomer of clavacin.[73] Even if penicillin itself is eventually synthesized, one wonders whether the cost of it will be lower than that of the natural penicillin now made.

66. Waksman, S. A., and Bugie, E.: Chaetomin, a New Antibiotic Substance Produced by Chaetomium Chochliodes, J. Bact. **48**:527-530 (Nov.) 1944.

67. Soltys, M. A.: Antibiotic Action of Aspergillus Fumigatus Against Mycobacterium Tuberculosis, Nature, London **154**:550-551 (Oct. 28) 1944. Asheshov, I. N., and Strelitz, F.: An Antibiotic Substance Active Against Mycobacterium Tuberculosis, Science **101**:119-120 (Feb. 2) 1945.

68. Sergiev, P. G.: Clinical Use of Gramicidin S, Lancet **2**:717-719 (Dec. 2) 1944. Gause, G. F., and Brazhnikova, M. G.: Gramicidin "S"; Its Origin and Mode of Action, Am. Rev. Soviet Med. **2**:134-138 (Dec.) 1944.

69. Hartley, G.; Enders, J. F.; Mueller, J. H., and Schoenbach, E. B.: Absence of Clinical Disease in Spite of a High Incidence of Carriers of Group A Hemolytic Streptococci of a Single Type: Failure of Tyrothricin to Influence the Carrier Rate, J. Clin. Investigation **24**:92-96 (Jan.) 1945.

70. Seegal, B. C., and Holden, M.: The Antibiotic Activity of Extracts of Ranunculaceae, Science **101**: 413-414 (April 20) 1945.

71. Weinstein, L., and MacDonald, A.: The Effect of Urea, Urethane and Other Carbamates on Bacterial Growth, Science **101**:44-45 (Jan. 12) 1945.

72. Stevenson, E. C., and Mitchell, J. W.: Bacteriostatic and Bactericidal Properties of 2, 4 Dichlorophenoxyacetic Acid, Science **101**:642-644 (June 22) 1945.

73. (*a*) Puetzer, B.; Nield, C. H., and Barry, R. H.: The Synthesis of a Clavacin Isomer, Science **101**:307-308 (March 23) 1945. (*b*) Warren, H. A.: Sulfadiazine Prophylaxis of Acute Infectious Diseases, J. Indiana M. A. **37**:447-451 (Sept.) 1944. (*c*) Hodges, R. G.: The Use of Sulfadiazine as a Prophylactic Against Respiratory Disease, New England J. Med. **231**:817-820 (Dec. 21) 1944.

CHEMOTHERAPY

Sulfonamide Prophylaxis of Diseases of the Respiratory Tract.—Glowing accounts of experience in the field of sulfonamide prophylaxis continue to appear. Both Warren and Hodges [73b,c] report striking decrease in the incidence of infections caused by hemolytic streptococci among about 10,000 men in each study who received 1 Gm. of sulfadiazine daily. While Warren [73b] and Coburn [74] report no effect on diseases caused by filtrable viruses, Hodges [73c] records a diminution in these as well. In two other studies,[75] sulfadiazine prophylaxis was used to prevent implantation of the hemolytic streptococcus on the mucous membrane and to control air-borne infection with this bacterium. In reading Coburn's report [75a] of observations on 600,000 subjects, one wonders how much hyperbole is involved when he writes: "Without chemoprophylaxis to prevent implantation of respiratory pathogens, the training programs of the U. S. Navy would have been impossible of maintenance." Mild reactions to sulfadiazine occurred in 0.5 per cent and severe reactions in 0.01 per cent, and 14 deaths probably related to the drug occurred. Similar statistics come from an Army source.[76] Sensitization to the drug did not appear to result from the small doses used prophylactically, and drug resistance of the streptococci did not develop, but in one camp hemolytic streptococci of types 17 and 19 were found to be resistant. Carter [77] states that at one place the incidence of scarlet fever, which varied between 63 and 171 per thousand, fell to 0 two weeks after prophylaxis began; tonsillitis fell from 426 to 46, and rheumatic fever from 87 per thousand to 0. He estimates that between $50,000,000 and $100,000,000 were saved by the procedure.

In a series of papers in the January issue of the *Annals of Internal Medicine,* Julianelle and Siegel report the effects of sulfonamide prophylaxis on acute infections of the respiratory tract. They gave sulfadiazine during fifteen weeks in the winter months to children in an

74. Coburn, A. F.: Mass Sulfadiazine Prophylaxis of Respiratory Infections in the U. S. Navy, Bull. New York Acad. Med. **21**:281-301 (June) 1945.

75. (*a*) Coburn, A. F.: The Control of Streptococcus Hemolyticus, Mil. Surgeon **96**:17-40 (Jan.) 1945. (*b*) Hodes, H. L.; Schwentker, F. F.; Chenoweth, B. M., and Peck, J. L.: Scarlet Fever as an Air-Borne Infection, Am. J. M. Sc. **209**:64-69 (Jan.) 1945.

76. Lee, R. V.: Reactions Following Mass Administration of Sulfadiazine, J. A. M. A. **126**:630-631 (Nov. 3) 1944.

77. Carter, T. J.: Mass Chemoprophylaxis at All Naval Training Stations, J. A. M. A. **127**:96 (Jan. 13) 1945.

institution, first 1 Gm. daily and then 2 Gm. daily, each child receiving a total of 148 Gm. Although mild infections of the respiratory tract and pneumonia were uncommon during this time, the number of attacks and the severity of both diseases were the same in the treated as in the control group. Purulent nasal discharge was the same in each group. Chickenpox also occurred equally in both. Toxic effects were negligible. The effects of sulfonamide drugs on the bacterial flora of the throat were of interest. The most striking was the rapid disappearance of gram-negative cocci and their gradual return even during treatment; those which reappeared had acquired tolerance for the drug. Hemolytic streptococci were only slightly affected. The presence of the indifferent and gamma streptococci in the throats of both the subjects and the controls indicated that these forms of the organism were uninfluenced by the drug. Of interest was the response of pneumococci. These, numerically at least, remained constant during treatment, but changes in the types present were striking. Although numerous types of pneumococci were present before treatment in the treated group and remained unchanged in the untreated group, those of the treated group changed greatly during therapy. Many of the types present before treatment disappeared, to be replaced almost entirely by types XI and XVIII. This change can be accounted for by the fact that pneumococci highly susceptible to the effects of sulfadiazine die off and others which are originally resistant or which develop resistance to the drug remain. Pneumococci which develop a high degree of resistance are unchanged in virulence or type specificity. After treatment is discontinued the distribution of types present before treatment returns.

A disturbing fact was that certain strains of bacteria which developed resistance to the drug in treated subjects were transmitted to children in the control groups.[78] Continuous sulfadiazine therapy was particularly accompanied with the appearance and spread of two drug-resistant strains, type 11 and type 18A. After therapy was discontinued, these types diminished in number but were still present in a few carriers for fourteen months. The development and spread of such drug-resistant pneumococci would be a hazard were it not for penicillin. As in studies on the hemolytic streptococcus discussed last year, the authors suggest that pneumococcic infection is precipitated not so much by the person's own normal bacterial residents as by new types suddenly acquired from outside sources.

Different results were obtained by other investigators [79] who, after using sulfonamide compounds in treatment, found sulfonamide-resistant pneumococci far less often than they expected to. Apparently none of the strains tested in their cases became resistant during treatment. Of the strains of pneumococci found before sulfonamide therapy, about 30 per cent persisted. As in studies previously mentioned, types of pneumococci not present before appeared during and after treatment.

In a paper by Plummer and others,[5] penicillin is judged to be more effective than sulfonamide compounds in the treatment of hemolytic streptococcus infection of the throat. In the author's experience severe infection caused by these bacteria occasionally occurred during treatment with sulfadiazine.

Treatment of Acute Infections of the Upper Respiratory Tract wth Sulfonamide Compounds.—According to Cecil,[80] neither the sulfonamide drugs nor penicillin are indicated in treating ordinary coryza or grip. They may be useful in rare instances when complications caused by drug-sensitive bacteria are present. For these, penicillin may entirely replace the sulfonamide compounds.

Sulfonamide Prophylaxis in Oral Surgery.—Bacteremia occurred in 25 of 30 patients (83 per cent) immediately after extraction of teeth, in Pressman and Bender's [81] experience. Str. viridans was most often present; Staphylococcus albus, the pneumococcus and the nonhemolytic streptococcus, occasionally. Of patients treated with sulfanilamide before extraction of teeth, 23 out of 30 (77 per cent) were found to have organisms in the blood on culture. Sulfanilamide obviously exerted no immediate quantitative effect on bacteria but reduced the numbers present in ten minutes. There was, however, some immediate qualitative effect. Aerobically sulfanilamide exerts no bacteriostatic effect on Str. viridans, but it does anaerobically. In another

78. Siegel, M.; Karr, H. V., and Julianelle, L. A.: The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides: V. Carrier Epidemic of Sulfonamide-Resistant Pneumococci, Am. J. Hyg. **41**: 228-241 (March) 1945.

79. Goodwin, R. A.; Wilcox, C., and Finland, M.: Persistence of Pneumococci in Sulfonamide Treated Cases of Pneumonia, Am. J. M. Sc. **209**:628-639 (May) 1945.

80. Cecil, R. L.: Chemotherapy in Acute Upper Respiratory Infections, Bull. New York Acad. Med. **21**: 263-277 (May) 1945.

81. Pressman, R. S., and Bender, I. B.: Effect of Sulfonamide Compounds on Transient Bacteremia Following Extracting of Teeth: I. Sulfanilamide, Arch. Int. Med. **74**:346-353 (Nov.) 1944.

study,[82] subacute bacterial endocarditis followed the extraction of a tooth from a patient with rheumatic heart disease despite sulfadiazine therapy three days before and three days afterward. In spite of a lack of supportive evidence, the authors still believe that "... the streptococcal focus in the teeth might even be etiologically significant in continuing the rheumatic activity."

Unless, as stated, the sulfonamide compounds actually do inhibit Str. viridans in an anaerobic milieu, there seems to be little to be hoped for in the prevention of subacute bacterial endocarditis by sulfonamide therapy. Perhaps prophylaxis with antibiotics will be more successful. Both would be successful if bacteria susceptible to their action were commonly found in the blood by operative procedures. At present dental extractions and tonsillectomies should be performed only if absolutely necessary on patients with valvular disease.

A description [83] is given of a method, said to be reliable enough to be of clinical value in the selection of therapy, for testing the susceptibility of group A hemolytic streptococci to sulfonamide compounds.

Sulfonamide Prophylaxis for Meningococcic Infections.—There is no longer doubt of the superiority of sulfonamide prophylaxis or therapy of meningococcic infections.[4] Prophylactic doses, however, cause only immediate cure or suppression of infection; the organisms soon return after treatment is stopped.[84] In treatment of meningitis, the response to penicillin is slower than the response to sulfadiazine; the carrier state persists, and there may be recurrences. In a report from Scotland [85] on over 2,000 cases, the mortality rate was reported as 17 per cent after treatment with sulfathiazole, sulfapyridine or sulfanilamide. One wonders why the reported rate is so much higher than that of many American series.

82. Clement, D. H., and Montgomery, W. R.: Subacute Bacterial Endocarditis: Report of a Case with Apparent Failure of Sulfonamide Prophylaxis Complicated by Massive Hemoperitoneum, Ann. Int. Med. **27**:274-282 (Feb.) 1945.

83. Wilson, A. T.: Method for Testing in Vitro Resistance of Group A Hemolytic Streptococci to Sulfonamides, Proc. Soc. Exper. Biol. & Med. **58**:130-133 (Feb.) 1945.

84. Phair, J. J., and Schoenbach, E. B.: IV. The Transmission and Control of Meningococcal Infections, Am. J. M. Sc. **209**:69-74 (Jan.) 1945.

85. Sulphonamides in the Treatment of Meningococcal Meningitis, Report to the Scientific Advisory Committee, Department of Health for Scotland, New York, British Information Services, 1944.

Local Therapy with Sulfonamide Compounds.—According to *Technical Bulletin* 147, March 1945, the War Department abandoned the local use of any chemical agent, including crystalline sulfonamide compounds, for their supposed effect in the prevention or treatment of infections. The local use of sulfonamide compounds in wounds after surgical operations, including those involving serous cavities, is not recommended. The decisions are of value in restraining the manufacture and needless waste of various sulfonamide dressings, lotions, ointments and emulsions.

CONTROL OF AIR-BORNE INFECTIONS

Robertson and his associates,[86] in a two year study of air-borne infections, show how environmental contamination by diseased persons or by carriers of pathogenic bacteria results in secondary reservoirs of infectious agents in bedding and floor dust, from which dried secretions bearing pathogenic agents are resuspended in the air in particulate form. A great increase in the numbers of air-borne streptococci follows bed making and sweeping, which probably constitute more important causes of contagion than does expulsion of "droplet nuclei" by infected persons. Measures to control such infections are designed to kill the pathogenic agents suspended in the air with bactericidal triethylene glycol vapor and by treatment of blankets, bedding, clothing and floors with oil to prevent the dispersal of dust bearing bacteria or viruses into the air.

The matter is the subject of a symposium published in the February issue of the *American Journal of the Medical Sciences.* Disinfection of air with propylene glycol and triethylene glycol causes a decrease in the incidence of infections of the respiratory tract, and in experimental studies ultraviolet rays reduced the incidence of air-borne tuberculosis in rabbits.

INFECTIONS OF THE RESPIRATORY TRACT

Viral Pneumonia (Viroid).—It is unfortunate that common usage has permitted the term "atypical pneumonia" to be so generally applied to one of the most common of diseases.[87] The word "atypical" means "not typical," but the disease is certainly typical in itself. Since its first presentation as a separate entity or syndrome

86. Robertson, O. H.; Hamburger, M.; Loosli, C. G.; Puck, T. T., and Lemm, H. M.: A Study of the Nature and Control of Air-Borne Infection in Army Camps, J. A. M. A. **126**:993-999 (Dec. 16) 1944.

87. Commission on Acute Respiratory Disease: I. Atypical Pneumonia, Am. J. M. Sc. **209**:55-58 (Jan.) 1945.

in 1938,[88] most evidence favored the view that one or more viruses were the cause, but, since the ultimate proof has not yet been attained in the majority of cases, many are timid about using the terms "virus" or "viral." When one judges from a comparison with known viral pneumonias, from the clinical and clinical pathologic behavior, from studies at necropsy[89] and from evidence that the disease can be transmitted to volunteers by inoculation with filtered secretions from patients,[90] what else can one believe but that agents now classified as filtrable viruses are operative?

Objection may be made even to the use of the term "pneumonia" in the name "viral pneumonia," since the same causative agent or agents give rise to far more mild attacks without pneumonia than to attacks with pneumonia. An analogy may be drawn with plague or tularemia; these infections are essentially systemic in nature although in certain cases the lungs show evidences of pneumonia; yet the terms "plague" and "tularemia" include all manifestations of either disease. It seems desirable, therefore, to employ an inclusive term, and elsewhere[91] I have proposed the word "viroid" to replace the meaningless name "atypical pneumonia" for the acute infections of the respiratory tract of unknown cause in question. "Viroid" has counterparts in "typhoid" and "varioloid." The term means "virus-like"; it includes all clinical varieties of the disease and is broad enough to allow for the possible existence of several implicated viruses. These can be named as they are eventually isolated and established as the causes of separate specific entities, as has already happened in the case of ornithosis, for example.

If the term "viroid" is tentatively used, the disease falls in line with the ones known as the common cold, grip and influenza,[92] each of which may at times include attacks of specific pneumonia. An etiologic arrangement would thus appear as follows:

Epidemic Forms	Sporadic Forms
Common cold	Psittacosis, ornithosis, ailurosis
Grip	Grip
Viroid	Viroid
Influenza A, B and Y (Stuart-Harris)	Lymphogranuloma venereum
	Lymphocytic choriomeningitis
	Varicella
	Vaccinia
	Variola
	Others

The confusion in terminology is further illustrated in a paper[93] discussing the resemblance of occasional attacks of "atypical" pneumococcic pneumonia to "atypical pneumonia." The cases of pneumococcic pneumonia presented were of the kind which first led to the use of the word "atypical." For patients from whom no pneumococci could be isolated from the sputum, "reverse" typing was done by testing the patients' serums every other day with the capsule-swelling test using stock pneumococci of fifty-six types. The authors point out the diagnostic difficulties which may arise. In certain instances pneumococcic pneumonia may resemble viral pneumonia in many respects, but in my experience confusion does not occur often. The point to emphasize is that every effort should be made to determine the cause in all cases of pneumonia, and if evidence of the activity of certain bacteria are found the patient should be promptly treated with penicillin, sulfadiazine or specific immune serum. There is always the probability that infection with drug-sensitive bacteria may be superimposed in viral pneumonias.

Etiologic Studies: There is still doubt as to whether the cat pneumonia viruses of Baker and of Howard cause diseases in human beings and of the importance of the mongoose-infecting virus discovered by Horsfall. In 1 case, Howard[94] succeeded in causing pneumonia in cats by inoculating them with oropharyngeal washings from patients with viral pneumonia, but it was uncertain whether the causative agent came from the

88. Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, J. A. M. A. **111**:2377-2384 (Dec. 24) 1938. Reimann, H. A., and Stokes, J.: An Epidemic Infection of the Respiratory Tract in 1938-1939: A Newly Recognized Entity, Tr. A. Am. Physicians **54**:123-129, 1939.

89. Golden, A.: Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined," Arch Path. **38**: 187-202 (Oct.) 1944.

90. (*a*) Commission on Acute Respiratory Diseases: Transmission of Primary Atypical Pneumonia to Human Volunteers, J. A. M. A. **127**:146-149 (Jan. 20) 1945. (*b*) Dingle, J. H.: The Present Status of the Etiology of Primary Atypical Pneumonia, Bull. New York Acad. Med. **21**:235-262 (May) 1945.

91. Reimann, H. A.: Atypical Pneumonia, Viral Pneumonia or Viroid Pneumonia? J. A. M. A. **127**: 543 (March 3) 1945.

92. Finland, M.; Parker, F.; Barnes, M. W., and Joliffe, L. S.: Acute Myocarditis in Influenza A Infections, Am. J. M. Sc. **209**:455-468 (April) 1945.

93. Racker, E.; Rose, S. P., and Turner, A. O.: Pneumococcic Pneumonia Resembling Primary Atypical Pneumonia, Am. J. M. Sc. **209**:496-502 (April) 1945.

94. Howard, M. E.; Blake, F. G., and Tatlock, H.: Feline Pneumonia Following Inoculation with Human Nose and Throat Washings, Federation Proc. **4**:147-148 (March) 1945.

patients or was latent in the cats, becoming activated by the procedure. In the other case,[95] further studies showed that mongooses could not be infected with material from patients with viroid among Army personnel, nor could they be infected with preserved material from previously sick mongooses.

Another point as yet apparently not considered is the possibility of a genuine etiologic relation of mouse meningopneumonitis virus and mouse pneumonitis virus[96] found in mice to human viroid. These viruses are native in mice, and when human secretions are injected into these animals for test, the development of disease in mice, if it occurs, is usually regarded as arising from an activation of virus already present in the animals. Why can this not be an actual transmission of a disease agent which is also operative in human beings? That both human beings and mice may be subject to the same diseases is suggested by an infection with meningopneumonitis infection virus contracted by a laboratory worker and by previous studies on lymphocytic choriomeningitis. More study is needed to settle this point.

A pneumonia virus was obtained from mice inoculated with materials from the lungs of human beings with pneumonia.[97] The lungs of mice with this infection contained an agent which specifically agglutinated mouse erythrocytes in a manner similar to the agglutination of chicken erythrocytes with influenza virus. Fluid from the lungs of a patient with pneumonia agglutinated homologous erythrocytes and guinea pig red cells as well, but not chicken erythrocytes.

The relation of streptococcus MG., or 344, to viroid is still mysterious. In Meiklejohn and Hanford's study,[98] agglutinin for this coccus was present in about 40 per cent of patients, but cold agglutination occurred in a greater number and neutralizing bodies usually appeared for a virus which was isolated from these patients. Many patients in whom these neutralizing bodies developed had no streptococcus agglutinin. Furthermore, in the successful transmission experiments commented on before, streptococcus agglutinins appeared only occasionally. A relation of the streptococcus to viroid is not evident. To account for the immunologic results with the streptococcus in question, it is suggested[90b] that various agents involved may have antigens in common or that changes in blood proteins during the disease may give rise to nonspecific reactions.

Four papers on viral pneumonia appear in the March issue of the *Journal of Clinical Investigation*,[99] representing conflicting views on a number of points. The naval group of investigators[100] again emphasize the possible role of Streptococcus MG (Rockefeller no. 344) in the pathogenesis of the disease and doubt the significance of the virus studied by the California group[99d] as a cause of the disease, since lesions in the lungs of animals caused by a variety of other agents were similar and none were further transmissible. The California group,[99c] on the other hand, report 16 cases of viral pneumonia presumably caused by their new virus, in most of which a cold agglutinin and neutralizing antibodies for the virus appeared during early convalescence. Among the volunteers of the Army investigating group[90] who apparently contracted viroid by inhaling filtered secretion from patients, none showed agglutinins for Streptococcus MG., and this streptococcus was not recovered in significant numbers from any of the subjects who received either unfiltered or filtered infectious material. This evidence is said to indicate that Streptococcus MG did not play a significant role in the disease transmitted to any of the volunteers.[90b] In 3 of the 10 volunteers a cold agglutinin developed after the disease.

The problem is obviously complicated, and much further study is needed. Curiously, no reference is made in any of the four papers to the early contribution on the subject[88] in which the names of the disease now commonly used (atypical pneumonia, virus pneumonia) were

95. Dammin, G. J., and Weller, T. H.: Attempts to Transmit Primary Atypical Pneumonia and Other Respiratory Tract Infections to the Mongoose, J. Immunol. **50**:107-114 (Feb.) 1945.

96. Eaton, M. D., and Van Herick, W.: Demonstration in Cotton Rats and Rabbits of a Latent Virus Related to Pneumonia Virus of Mice, Proc. Soc. Exper. Biol. & Med. **57**:89-92 (Oct.) 1944.

97. Mills, K. C., and Dochez, A. R.: Specific Agglutination of Murine Erythrocytes by a Pneumonitis Virus in Mice, Proc. Soc. Exper. Biol. & Med. **57**:140-143 (Oct.) 1944.

98. Meiklejohn, G., and Hanford, V. L.: Agglutination Tests with Streptococcus No. 344 in Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **57**:356-358 (Dec.) 1944.

99. (*a*) The Commission on Acute Respiratory Diseases: An Experimental Attempt to Transmit Primary Atypical Pneumonia in Human Volunteers, J. Clin. Investigation **24**:175-188 (March) 1945. (*b*) Curnen, E. C.; Mirick, G. S.; Ziegler, J. E.; Thomas, L., and Horsfall, F. L.: Studies on Primary Atypical Pneumonia: I. Clinical Features and Results of Laboratory Investigations, ibid. **24**:209-226 (March) 1945. (*c*) Thomas, L.; Mirick, G. S.; Curnen, E. C.; Ziegler, J. E., and Horsfall, F. L.: II. Observations Concerning the Relationship of a Non-Hemolytic Streptococcus to the Disease, ibid. **24**:227-240 (March) 1945. (*d*) Meiklejohn, G.; Eaton, M. D., and van Herick, W.: A Clinical Report on Cases of Primary Atypical Pneumonia Caused by a New Virus, ibid. **24**:241-250 (March) 1945.

100. The Commission on Acute Respiratory Diseases.[99a] Curnen.[99b] Thomas and others.[99c]

first suggested, the disease was established as a distinct entity, the first studies implicating a virus as the etiologic agent were described, a resemblance to psittacosis was pointed out, the clinical course was described (including the delayed pulmonary signs, bradycardia, nervous manifestations, roentgenographic changes, paucity of complications and ineffectiveness of sulfonamide compounds) and, finally, in which it was pointed out that the pneumonic forms may represent only the severe forms of a frequently mild epidemic infection of the respiratory tract. All of these points have been confirmed, and little of clinical importance has since been added despite the enormous amount of work done.

Cold Agglutination: Numerous reports of studies on cold agglutination of erythrocytes during the disease have appeared. It seems that the reaction occurs in many conditions and diseases but more often and in higher titers in viroid. Titers higher than 1:160 are seldom found in other diseases but are common in severe viroid. The reactions may persist in high dilution for many months after an attack and may appear and disappear in persons without evident infection.[101] Yet the reaction was present in only 55 per cent of cases reported in one study,[102] and in only 31 per cent was the titer higher (1:64 or more) than that which occurs in other common infections. The titer is often in proportion to the severity of the disease. Cold agglutination developed in most of the experimentally infected volunteers.[90] In another report,[103] cold agglutination is said to have appeared eight to twelve days after the onset of the disease. The causative factor lay in the globulin fraction, implicating an antigen-antibody reaction. During one epidemic all patients showed a cold agglutinin; in another the reaction was not consistently present. The reaction is helpful in diagnosis only when it is strongly positive and aids in differentiating viroid from other diseases, especially from bacterial pneumonia, pulmonary tuberculosis and the psittacosis-ornithosis group of infections.

Clinical Observations: From many clinical reports during the past year very little new information has accrued. The possibility of the development of bronchiectasis is discussed[104] but probably is not important. I have not yet encountered bronchiectasis as a sequel. The bronchial walls may be dilated, but other evidence of bronchiectasis was not present in studies made at necropsy.[89] In patients in which it does occur, the possibility of preexisting latent bronchiectasis must always be considered. Fractures of ribs from excessive severe coughing occurred in 19 of 500 patients in one series studied,[105] and so in case of excessive pain in the chest in patients with the disease this accident must not be mistaken for pleurisy, which is an uncommon accompaniment. One may question the statement in one paper[106] that viroid pneumonia "is not a contagious disease." In the same paper, complications of meningitis, pleural effusion and "aputrid" pulmonary abscess are reported, but on poor evidence. The only indications of meningitis were a few doubtful neurologic signs and the presence of 33 lymphocytes in one sample of spinal fluid; pleural effusion and abscess were diagnosed on the basis of uncertain roentgenographic appearances alone.

Treatment: In spite of all advice to the contrary, sulfonamide therapy is still widely employed for viroid. One author[107] writes that sulfonamides were actually given as a therapeutic diagnostic test. Certainly better methods of diagnosis are in order. Penicillin, likewise shown to be ineffective against viral infections,[3a] is said to give good results,[108] but the report is unconvincing; no controls were observed.

Varying Forms of Viral Pneumonia: Two fatal cases of influenza associated with bacteria-free pneumonia are described.[92] Influenza virus A was obtained from the pneumonic areas at necropsy, giving further proof that a viral form of pneumonia occurs in true influenza.

A small outbreak of a severe form of a psittacosis-like disease, with 8 deaths in 19 known cases, occurred in Louisiana.[109] The disease can

101. Favour, C. B.: Autohemagglutinins—"Cold Agglutinins," J. Clin. Investigation **23**:891-897 (Nov.) 1944.

102. Commission on Acute Respiratory Diseases: Cold Hemagglutinins in Primary Atypical Pneumonia and Other Respiratory Infections, Am. J. M. Sc. **208**: 742-750 (Dec.) 1944.

103. McNeil, C.: The Relationship of Cold Agglutinins to the Cause of Primary Atypical Pneumonia, Am. J. M. Sc. **209**:48-54 (Jan.) 1945.

104. Kay, E. B.: Bronchiectasis Following Atypical Pneumonia, Arch. Int. Med. **75**:89-104 (Feb.) 1945.

105. Harvey, R. M.: Rib Fractures in Atypical Pneumonia, Am. J. Roentgenol. **52**:487-493 (Nov.) 1944.

106. Glendy, R. E.; Beaser, S.B., and Hankins, W. D.: Primary Atypical Pneumonia of Unknown Cause, with Unusual Manifestations and Complications, Arch. Int. Med. **75**:30-38 (Jan.) 1945.

107. Gunderson, S.: Primary Atypical Pneumonia of Unknown Etiology, New England J. Med. **231**:697-700 (Nov. 23) 1944.

108. Short, J. J.: Penicillin in the Treatment of Primary Atypical Pneumonia, U. S. Nav. M. Bull. **43**: 974-980 (Nov.) 1944.

109. Olson, B. J., and Treuting, W. L.: An Epidemic of a Severe Pneumonitis in the Bayou Region of Louisiana: I. Epidemiological Study, Pub. Health Rep. **59**:1299-1311 (Oct. 6) 1944. Treuting, W. L., and Olson, B. J.: II. Clinical Features, ibid. **59**:1331-1356 (Oct. 13) 1944. Binford, C. H., and Hauser, G. H.:

(Footnote continued on next page)

probably be included with the sporadic forms of viral pneumonia, since no mild forms of it were recognized. It was thought to have been spread from person to person as an air-borne infection, but the source of the disease is unknown. A virus was readily isolated by the intraperitoneal or intranasal inoculation of mice with washings from the throats and with material from the lungs of patients studied at necropsy. It appeared to belong to the psittacosis group of pathogens. One of my own patients with a severe attack of psittacosis or ornithosis had shot quail in South Carolina ten days before the onset of illness. This occurrence suggests the possible existence of ornithosis in game birds.

Report [110] was made of diagnosis of 6 cases of ornithosis on the inadequate basis of a single positive complement fixation reaction in each instance and of possible contact with pigeons. Diagnosis can be accepted tentatively only if the tests show a rise of titer and then a fall after the disease and if there was reasonable proof of contact with infected birds; positive diagnosis can be made only if the agent is isolated and identified. Reports like this one confuse the issue and should not be published.

Pinkerton and his co-workers [111] report a subacute or chronic form of pneumonia in infants, characterized by large multinucleated cells and cytoplasmic and intracellular inclusions in the pulmonary tissues. The histologic reactions resemble those seen occasionally in measles and in canine distemper and are different from those in the pneumonia of infants described by Goodpasture and by Adams. The studies suggest the need for investigating the possibility that human viral pneumonia can be contracted from dogs with distemper.

Other Forms of Pneumonia.—Interest is increasing in transitory pulmonary infiltrations associated with eosinophilia, often called Loeffler's syndrome.[112] It would seem that the condition may occur as a result of allergic sensitization to the products of many parasites, including ascaris, liver fluke and Endamoeba histolytica. Perhaps any prolonged mild infection associated with allergic phenomena may cause the syndrome.

Pneumonia in Association with Malaria.—When pneumonia occurs with malaria, it is often difficult to decide whether it is of bacterial or viral origin or is a manifestation of malaria itself. Most observers do not believe that a specific malarial pneumonia occurs but believe that the pulmonary disturbance is caused by blockage of vessels with disintegrated red cells, by atelectasis or by other factors. In one series of patients,[113] pneumonia was diagnosed for 3.7 per cent. The symptoms resembled those of viroid pneumonia. British clinicians regard the relation of viral pneumonia to malaria as fortuitous.[114]

Wood and Pierson [115] studied 1 of the rare cases, or at least 1 of the rarely recognized cases, of pulmonary adenomatosis. The lesion in the lung was a diffuse alveolar epithelial hyperplasia resembling noncaseating disseminated miliary tuberculosis and also resembling the disease called epizootic adenomatosis, or *jaagsiekte*, occurring in sheep and other animals. Their observations raise a number of important questions: (1) whether the disease in human beings is related to that in sheep; (2) whether a virus may be the cause, giving rise to a tumor-like hyperplasia like that caused by Shope's papilloma virus; (3) whether the cells lining the alveoli are epithelial in nature, and (4) whether there is a possibility that the disease is not so rare as is believed and may be mistakenly diagnosed as pulmonary cancer.

Influenza.—Shope [116] reviews the developments in the knowledge of influenza. He reiterates his own theory that human influenza was transmitted to hogs during the pandemic of 1918. The virus of hog influenza, if it was related to that outbreak, as it seems to have been is the only proof of the identity of the disease with influenza as it is now understood. One wonders, however, if hogs have been infected only since 1918, as Shope suggests. They certainly must have been exposed to the pandemic of 1889 and to previous ones and, like human beings, perhaps served as occasional reservoirs of infection. Both would seem to be able to serve as mutual

III. Pathological Observations, ibid. **59**:1363-1373 (Oct. 13) 1944. Olson, B. J., and Larson, C. L.: IV. A Preliminary Note on Etiology, ibid. **59**:1373-1374 (Oct. 20) 1944.

110. Levinson, D. C.; Gibbs, J., and Beardwood, J. T.: Ornithosis a Cause of Sporadic Atypical Pneumonia, J. A. M. A. **126**:1079-1084 (Dec. 23) 1944.

111. Pinkerton, H.; Smiley, W. L., and Anderson, W. A. D.: Giant Cell Pneumonia with Inclusions, Am. J. Path. **21**:1-15 (Jan.) 1945.

112. Transitory Pulmonary Infiltration Associated with Eosinophilia—Loeffler's Syndrome, editorial, J. A. M. A. **126**:837 (Nov. 25) 1944.

113. Applebaum, I. L., and Shrager, J.: Pneumonitis Associated with Malaria, Arch. Int. Med. **74**:155-162 (Sept.) 1944.

114. Fleming, J.; Lindeck, E. W., and Evans, I. H.: "Primary Atypical Pneumonia": An Epidemic Associated with Malaria, Brit. M. J. **1**:689-693 (May 19) 1945.

115. Wood, D. A., and Pierson, P. H.: Pulmonary Alveolar Adenomatosis in Man: Is This the Same Disease as Jaagsiekti in Sheep? Am. Rev. Tuberc. **51**:205-224 (March) 1945.

116. Shope, R. E.: Old, Intermediate and Contemporary Contributions to Our Knowledge of Pandemic Influenza, Medicine **23**:415-455 (Dec.) 1944.

transmitters, to begin or to propagate epidemics in either or both species.

British views on influenza are summarized by Stuart-Harris.[117] In many epidemics in England during the past few years various combinations of influenza A, B and unknown forms occurred. In one epidemic 50 per cent of attacks were of unknown cause but were called influenza Y. There are three theories to account for this Y type of infection: (*a*) It is caused by one or more as yet unknown viruses; (*b*) it is caused by the basic virus of influenza, devoid of antigenic ability, and (*c*) it is caused by either type A or type B virus, which for some unknown reason cannot be isolated and gives rise to no serologic response.

Epidemics are unpredictable, as is shown by the author's mistake in predicting a large outbreak: In spite of the prevalence of influenza virus A in 1941, the vast disorganization caused by aerial bombing was not accompanied with an anticipated epidemic. In fact, influenza is the only important epidemic disease unaffected thus far by the war.[118]

Acute collapse of the circulatory system and a shocklike state have long been recognized as serious complications or sequelae of influenza and of viral pneumonia. They were thought to be caused by some toxic effect on the central nervous system or on the heart itself. Finland and his associates[92] review the information on the subject and describe 2 cases of their own. Both patients had influenza, and at necropsy bacteria-free pneumonitis and acute myocarditis were found. Influenza virus A was thought to have caused the myocardial lesions.

Prevention of Influenza: In discussing the prospects of preventing epidemics of influenza, one author believes in the use of all procedures available, including general measures of hygiene, aerial disinfection, quarantine and vaccine. If a virus of different characteristics from that against which vaccines are available were operative, vaccine would not help unless the current virus were used as an antigen.

Attempts to improve influenza vaccine are being made.[119] The use of Hirst's concentrated vaccine reduces the attack rate but not enough to be of practical value. Vaccine, if it is used at all, is best given early in an outbreak after its identification; if given in anticipation of an outbreak it may be wasted, since outbreaks of influenza are unpredictable and immunity is of brief duration. Stanley[120] describes a successful procedure of centrifugation for the production of concentrated vaccine in large amounts. Other studies show that the immunizing effect on mice of formaldehyde-treated influenza virus can be enhanced and prolonged by precipitation of the virus on calcium phosphate.[121]

The intraperitoneal injection of atropine sulfate before the intranasal inoculation of influenza virus in mice decreases the incidence and extent of infection of these animals.[122]

Other Studies on Influenza: According to Hirst,[123] the most sensitive method to recover influenza virus is through the inoculation of chick embryos by the allantoic route with throat washings containing penicillin to suppress bacterial growth. Eaton and his associates,[124] however, found the chick embryo technic to be quicker but less reliable than the technic of inoculation of either hamsters or ferrets. Others,[125] using the chick embryo method, record the important finding of influenza virus in the throats of 5 of 13 healthy persons who had been in contact with patients suffering from influenza A. In 9 of the 13 studied, significant increase of antibodies to influenza virus A appeared according to the test of inhibition of agglutination of red blood cells. In 3 of those from whom the virus was isolated, no antibodies developed. The results verify an old concept that some healthy persons carry the virus and may be of great importance in the spread of influenza.

The question arises[126] as to whether influenza virus causes neurologic disturbances by actually

117. Stuart-Harris, C. H.: Influenza and the Influenza Viruses, Brit. M. J. **1**:207-216 (Feb. 17); 251-257 (Feb. 24) 1945.

118. Stowman, K.: The Epidemic Outlook in Europe, J. A. M. A. **128**:185-188 (May 19) 1945.

119. Hirst, G. K.; Rickard, E. R., and Friedewald, W. F.: Studies in Human Immunization Against Influenza: Duration of Immunization Induced by Inactive Virus, J. Exper. Med. **80**:265-273 (Oct.) 1944.

120. Stanley, W. M.: The Preparation and Properties of Influenza Virus Vaccines Concentrated and Purified by Differential Centrifugation, J. Exper. Med. **81**: 193-217 (Feb.) 1945.

121. Salk, J. E.: The Immunizing Effect of Calcium Phosphate Adsorbed Influenza Virus, Science **101**: 122-124 (Feb. 2) 1945. Stanley, W. M.: The Precipitation of Purified Concentrated Influenza Virus and Vaccine on Calcium Phosphate, ibid. **101**:332-335 (March 30) 1945.

122. Wheeler, A. H., and Nungester, W. J.: The Effect of Atropine Sulfate on the Course of Influenza Virus Infection, Science **100**:523-524 (Dec. 8) 1944.

123. Hirst, G. K.: Direct Isolation of Influenza Virus in Chick Embryos, Proc. Soc. Exper. Biol. & Med. **58**: 155-157 (Jan.) 1945.

124. Eaton, M. D.; Corey, M.; van Herick, W., and Meiklejohn, G.: A Comparison of Various Methods of Demonstrating Influenza Virus in Throat Washings, Proc. Soc. Exper. Biol. & Med. **58**:6-9 (Jan.) 1945.

125. Crowley, J. H.; Thigpen, M. P., and Riekard, E. R.: Isolation of Influenza A Virus from Normal Human Contacts During an Epidemic of Influenza A, Proc. Soc. Exper. Biol. & Med. **58**:345-356 (Dec.) 1944.

126. Henle, G., and Henle, W.: Neurological Signs in Mice Following Intracerebral Inoculation of Influenza Viruses, Science **100**:410-411 (Nov. 3) 1944.

growing in brain tissue or by its toxicity in a manner similar to that of the psittacosis group of pathogens, as reported by Rake and Jones last year.

One author,[127] impressed by certain reports of reduction of the incidence of colds by sulfonamide prophylaxis, argues that colds therefore are not caused by viruses. Without evidence for his assumption, he writes that most colds are caused by streptococci; that is, the Str. viridans dissociates into pathogenic hemolytic streptococci. Such transformation is not known to occur. Other vacuous arguments are also presented, but his views are contrary to general opinion.

Pneumococcic Pneumonia.—Speransky, a Russian, basing his idea on the reaction in rabbits' lungs after intracranial trauma, believes that human pneumonia results from stimuli originating in the central nervous system.[128] This theory is cited as a reason for the sudden beginning of lobar pneumonia. Because sulfonamide therapy gave unfavorable results, he recommends the subcutaneous injection of procaine hydrochloride solution into the area of the rhomboid muscles for "its neurotrophic effect." Within eighteen to twenty-four hours after injection, recovery is said to occur. The line of reasoning is suggestive of osteopathic theories. The author makes no mention of studies on the pathogenesis of pneumonia by American or other scientists. However, regardless of Speransky's logic, others [129] have also felt that nervous influence may play an important role in lobar pneumonia in accounting for both its sudden onset and its sudden ending, but in a different manner.

Ginsburg,[130] adopting Speransky's suggestion, reports good results in treating thyrotoxicosis, nephritis, pneumonia and other diseases with his method. From his 49 cases of pneumonia, some of the charts look impressive; recovery occurred twelve to forty-eight hours after the injection of procaine hydrochloride, but the data given are so meager as to render critical judgment difficult; only 1 death occurred. No laboratory studies except leukocyte counts were made, because of war conditions. The work needs confirmation, to say the least.

127. Brown, E. E.: Common Cold Not Caused by Virus, Northwest Med. **44**:39-41 (Feb.) 1945.

128. Speransky, A. D.: Experimental and Clinical Lobar Pneumonia, Am. Rev. Soviet Med. **2**:22-27 (Oct.) 1944.

129. Reimann, H. A.: The Pneumonias, Philadelphia, W. B. Saunders Company, 1938, p. 183.

130. Ginsburg, E. M.: Pathogenesis and Treatment of Lobar Pneumonia, Am. Rev. Soviet. Med. **2**:28-36 (Oct.) 1944.

Diphtheria.—Diphtheria is the leading epidemic disease in war-torn Europe.[131] More than 1,000,000 cases occurred in 1943. The most serious development is not so much the spread of the disease as its change in type, increased severity and resistance to antitoxic treatment. In Germany [131a] one third of the population of a large city were considered to be carriers. Healthy carriers are responsible for almost all cases. In Baltimore,[132] fortunately, the gravis type of diphtheria has not been more prevalent than heretofore.

Coccidioidomycosis.—This infection continues to be of importance, especially among military personnel stationed in western areas where the disease is endemic.[133] In certain camps cutaneous reactions to the specific antigen developed in 80 per cent of the inhabitants after exposure to infection. In the great majority of instances the infection is so mild as to be unrecognized; in certain patients the symptoms are those of a mild infection of the respiratory tract and in others of pulmonary tuberculosis. In rare cases the chronic or severe granulomatous stage develops. The advanced forms seem to be much more likely to develop in Negroes. Basal meningitis occasionally occurs in coccidioidomycosis. A case is described [134] in which the outstanding lesions of the disease were in the brain.

Men exposed to infection in an area where the disease is endemic may go elsewhere, and the disease may develop in places where it would not be thought of or diagnosed unless special diagnostic tests were made. There is no satisfactory treatment.

Histoplasmosis.—Palmer [135] made a survey in order to learn the cause of pulmonary calcification not related to tuberculosis or to coccidioidomycosis. In a study of 3,000 persons, of whom 294 had pulmonary calcification, 23 per cent had a positive reaction to histoplasmin, a filtrate of broth culture of Histoplasma capsulatum. Great

131. (*a*) Kollath, W.: Problems of Diphtheria, Deutsche med. Wchnschr. **70**:203-204 (April) 1944. (*b*) Stowman.[118]

132. Frobisher, M.; Adams, M. L., and Kuhns, W. J.: Characteristics of Diphtheria Bacilli Found in Baltimore Since November 1942, Proc. Soc. Exper. Biol. & Med. **58**:330-334 (April) 1945.

133. Lee, R. V.: Coccidioidomycosis in Western Flying Training Command, California & West. Med. **61**:133-134 (Sept.) 1944. Denenholz, E. J., and Cheney, G.: Diagnosis and Treatment of Chronic Coccidioidomycosis, Arch. Int. Med. **74**:311-330 (Nov.) 1944.

134. Schlumburger, H. G.: A Fatal Case of Cerebral Coccidioidomycosis with Cultural Studies, Am. J. M. Sc. **209**:483-496 (April) 1945.

135. Palmer, C. E.: Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin, Pub. Health Rep. **60**:513-520 (May 11) 1945.

differences in the percentage of reactions were noted between those from Minnesota (6 per cent) and from Missouri (66 per cent). These results suggest that histoplasmosis is endemic in certain regions and may be a frequent cause of pulmonary calcification and that the disease may be far more common in mild form than it is believed to be. Parsons and Zarafonetis [136] review 71 cases of histoplasmosis and the subject in general. The infection is apparently worldwide in distribution, and cases are being recognized with increasing frequency. (The infection is not spreading.) The symptoms and signs often resemble those of many other diseases, and correct diagnosis may not be made unless biopsy, culture and other types of examinations are done. There is no specific treatment for the disease. It is reported that most cases end fatally. This observation is probably wrong in view of those made by Palmer.[135] The severest and fatal cases are most apt to be diagnosed; mild ones may escape notice and diagnosis.

Another spontaneous case of histoplasmosis in a dog is reported.[137] A disease thought to be histoplasmosis in a cat on further study was diagnosed as toxoplasmosis.[138] In about 3 per cent of adults in St. Louis, evidence of previous infection was present in the serum.[139]

Pulmonary Tuberculosis.—In the light of certain studies on coccidioidomycosis and histoplasmosis just mentioned, doubt may be cast on observations [140] reported from San Antonio, Texas, which is said to have the highest tuberculosis rate in this country but which is in a region where coccidioidomycosis is endemic. In this study, diagnosis of tuberculosis was made for about 5 per cent of 20,000 residents on the basis of a roentgenographic survey alone. Obviously there is need of reinvestigation of the data. In Los Angeles, for example, the incidence of positive coccidioidin cutaneous reactions in one group studied was 26 per cent.[141] At necropsy several patients who had given a positive reaction all revealed healed calcified lesions indistinguishable from those of tuberculosis. Another disease which may at times easily be mistaken for pulmonary tuberculosis is paragonimiasis,[142] which may be encountered especially among returned war veterans. In this disease, chronic cough, pain in the chest and bloody sputum are common.

None of the sulfonamide drugs now available has given any clinical therapeutic effect sufficiently encouraging to warrant its use in the treatment of tuberculosis.[143] The same may be said at present for various antibiotics thus far tested.

Experimentally Produced Diseases of the Respiratory Tract.—In extensive studies, Melville and Stehle [144] tested the effect of seventy-nine chemical compounds, including sixty-one aminobenzine derivatives, on experimental tuberculosis in guinea pigs. None of the agents tested showed any evidence of curative action, since in all experiments gross evidence of tuberculosis could still be detected in all treated and untreated animals no matter how long they survived.

An attack of pneumonic plague contracted during laboratory research is reported.[145] The patient recovered after a stormy course, during which he received sulfadiazine and penicillin, but it is uncertain that recovery can be ascribed to either. No secondary or contact attacks occurred among associates or attendants. The patient had received antiplague vaccine one year before, but six months later his serum contained no demonstrable protective bodies. Plague pneumonia is generally believed to be uniformly fatal, but it is safe to guess that numerous undiagnosed cases end in recovery. It would be of great interest to test the effects of streptomycin in plague.

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142. Miller, J. J., and Wilbur, D. L.: Paragonimiasis (Endemic Hemoptysis), U. S. Nav. M. Bull. **42**:108-110 (Jan.) 1944.

143. Hinshaw, H. C.; Feldman, W. H., and Pfuetze, K. H.: Present Status of Chemotherapy in Tuberculosis, Ann. Int. Med. **22**:696-703 (May) 1945.

144. Melville, K. I., and Stehle, R. L.: Chemotherapy in Experimental Tuberculosis, Canad. J. Research **22**: 95-121 (Dec.) 1944.

145. Minter, E. J.: Pneumonic Plague: Report of a Case with Recovery, J. A. M. A. **128**:281-283 (May 26) 1945.

(To Be Concluded)

Book Reviews

Essentials of Allergy. By Leo H. Criep, M.D. Price, $5. Pp. 381, with 42 illustrations and 1 plate in color. Philadelphia: J. B. Lippincott Company, 1945.

As its title implies, this small book deals with the important aspects of allergy. Packed into the volume are chapters on the immunology of allergy, anaphylaxis and serum sickness, diagnosis and treatment of allergy in general and of each allergic disease, with special emphasis on bronchial asthma, hay fever and allergy of the skin. Other allergic conditions are also considered. Because of limitation of space, the outline form of discussion is used. The book is exceedingly well written and full of clear and concise information of special interest for medical students and general practitioners, and even for allergists. Reports of cases illustrate teaching points. The section on bronchial asthma and its relation to the heart is especially good, as is also that on psychosomatic aspects in treatment.

A few minor corrections should be noted. The author might well have been more emphatic in stating that true migraine is almost always due to food allergy and should therefore be investigated from the viewpoint of allergy. He states that "roentgen ray therapy has not proved its value in the treatment of bronchial asthma." Many workers have shown that this method does give good, though only temporary, results. His suggestion that 50 per cent sucrose should be injected intravenously in status asthmaticus should not be followed; it is known that such treatment usually harms the kidneys. He states that "there is no eosinophilia" in patients with intrinsic asthma, that is, asthma with negative cutaneous reactions. Most investigators have found only a little difference between the percentage of eosinophils in persons with extrinsic and with intrinsic asthma. Also, most men who have experience with both the scratch and the intradermal method of skin testing will not agree with his opinion that intradermal testing is "less painful" than the scratch method. With these minor exceptions, the book is excellent throughout and should be widely used. As the author states, larger volumes on the subjects should also be consulted.

Clinical Case-Taking. By George R. Herrmann, M.D. Third edition. Price, $1.75. Pp. 192. St. Louis: The C. V. Mosby Company, 1945.

This is a manual of procedure for ward and bedside practice. Several pages are devoted to the plan, scope, objectives, principles, art and technic of case taking, and these are followed by several chapters of detailed directions for history taking and for physical examination. More than half of the volume is composed of chapters on semiology of diseases and systems. Apparently the purpose of these chapters is to familiarize the student with terminology and to point out the common symptoms and findings of some diseases. The book should be of value to the beginner in physical diagnosis.

Duodenal and Jejunal Peptic Ulcer. By Rudolf Nissen, M.D. Price, $4.75. Pp. 143, with 123 illustrations. New York: Grune & Stratton, Inc., 1945.

The reviewer has little to add to the comments of Wangensteen in his foreword to this little book. While he deals largely with the technic of various operations, the author also presents with reasonable logic his rationale for one or another procedure. None the less it is clear that the whole subject of operation for duodenal ulcer remains a complex one, and the exact reasons for relief and failure are often difficult to evaluate and must be involved with the psychologic aspects of the situation. There are many excellent illustrations and a bibliography.

News and Comment

1945 MEETING OF THE MISSISSIPPI VALLEY MEDICAL SOCIETY CANCELED

The 1945 meeting of the Mississippi Valley Medical Society, which was to be held in St. Louis in September, has been canceled because of war restrictions. Plans are being made to hold the 1946 meeting at the Jefferson Hotel in St. Louis September 25 through 27.

Correspondence

PERNICIOUS ANEMIA IN CHINESE

To the Editor:—Dr. Chester S. Keefer was good enough to call to my attention an error which Dr. Rappolt and I had made in citing Dr. Yang and himself in our article in the June 1945 issue of the ARCHIVES (p. 404). In this article we said: "Yang and Keefer have reported the only 2 cases of pernicious anemia in Chinese observed previously on this continent. They were cases of Minot's and apparently were typical." Yang and Keefer have reported 2 cases of pernicious anemia in Chinese patients, but these were observed in Peiping, China. In their article they refer to a case which Minot had observed in the United States. This case was not observed by them and has not been reported by Minot.

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